

Physicians' prescribing of anti-hypertensive combinations in a tertiary care setting in southwestern Nigeria.

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ABSTRACT -- Purpose: To evaluate physicians' prescribing of anti-hypertensive drug combinations in a tertiary care setting in southwestern Nigeria, determine the degree of usage of Angiotensin Converting Enzyme (ACE) inhibitor-based combinations and identify specific points of intervention to improve outcomes of anti-hypertensive combination therapy. **Methods:** A cross-sectional retrospective drug use review was conducted between June 1st and August 31st 2002 using randomly selected 200 case notes of patients attending the Hypertension Clinic at a 900-bed tertiary care facility in southwestern Nigeria. 11 case notes were not used due to incompleteness. **Results:** 73% (138) of the patients were on anti-hypertensive drug combinations, comprising 71.7% (99), 24.4% (34) and 3.6% (5) on combinations of two, three and four drugs respectively. Overall, Thiazide diuretic consisting mainly of fixed dose combination of Amloride and Hydrochlorothiazide (Moduretic®) was the most frequently prescribed drug class in anti-hypertensive combination therapy (83.3%). ACE inhibitor, Lisinopril (Zestril®), was prescribed in combination with Moduretic®, Calcium channel blocker and beta-blocker in 6.5%, 8.5% and 0.7% respectively. Blood pressure control was adequate in only 29% (40) of patients, though adherence with therapy was documented as adequate in 77.5% (107). Type-2 diabetes mellitus (32.7%) and osteoarthritis (21.8%) were the most frequent co-morbidities. Potentially harmful drug-drug interactions in the study sample were identified in 17.5% (46) of patients. Physician documentation of adverse drug reactions among patients was done in only 10.9% of cases. There appear to be no institutionalised system

in place to monitor, detect and document adverse drug reactions among patients on anti-hypertensive drug therapy. **Conclusion:** Physicians' prescribing of anti-hypertensive drug combinations in a tertiary care setting in southwestern Nigeria is considerable. However, this practice does not appear to have positively impacted on blood pressure control among hypertensive patients nor being modulated by an Institutionalised standard guide.

INTRODUCTION

The use of any of the main anti-hypertensive drug classes as monotherapy at the recommended doses has been shown to produce similar blood pressure reduction (1). Studies have shown that good blood pressure control, below 140mmHg (systolic) and 90mmHg (diastolic) is achieved in only a minority of patients on anti-hypertensive monotherapy (1-3). Majority of patients will require combination of anti-hypertensive drugs to achieve good blood pressure control (3-5). Several studies have documented the long term benefits of use of anti-hypertensive combinations in high risk population such as black hypertensives who are usually at increased risk of morbidity and mortality from cerebrovascular and cardiovascular events (6-11). Furthermore, black hypertensives have higher incidences of concurrent diseases such as left ventricular hypertrophy, congestive cardiac failure, diabetes mellitus and chronic renal failure and have been shown to benefit from use of anti-hypertensive drug combinations (12-15). Anti-hypertensive combinations will however be inimical in situations where drugs that act through similar mechanism, hence do not contribute to blood pressure reduction, or drugs that have similar side effects are combined. Such combinations usually result in inadequate blood pressure control and increased risk of adverse effects (1,2,16,17).

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Guidelines resulting from evidences from prospective studies have been produced by national and international bodies to aid clinicians, irrespective of resource settings, in selecting anti-hypertensive combinations that is most likely to be beneficial to majority of patients (1,2,5,16). These guidelines recommends that if patients do not attain adequate blood pressure control (Systolic/Diastolic blood pressure $\leq 140/90$ mmHg) with monotherapy with any of the agents within the Angiotensin Converting Enzyme (ACE) inhibitors (A) and Beta blocker (B) or Calcium antagonists (C) and Diuretics (D), effective combinations that will ensure optimal blood pressure reduction is achieved by adding one pair of A and B to one pair of C and D. However these guidelines are not rigid and the choice of anti-hypertensive combinations to be used will probably be influenced by peculiar local factors such as, for example, socio-economic factors, affordability and accessibility to anti-hypertensive drugs and care in resource-limited settings (1,3,18).

Several studies have shown that morbidity and mortality due to severe and malignant hypertension is high among Nigerians (19-23). This has been attributed to combination of factors such as late presentation for treatment often with possible end-organ damage, delayed diagnosis and commencement of treatment, inadequate blood pressure control in majority of patients on treatment, inadequacy of pharmacological treatment and patient non-adherence with drug therapy (21,22,24-29). The objective of this study is to evaluate the physicians' prescribing practices with regards to the use of anti-hypertensive drug combinations among hypertensive patients in southwestern Nigeria, determine the degree of usage of Angiotensin Converting Enzyme (ACE) inhibitor-based combinations and identify specific points of future intervention to improve the use of combination therapy.

METHODS

The study was conducted between June 1st and August 31st 2002 at the Medical Outpatient Clinic of a 900-bed tertiary care hospital (University College Hospital) located at Ibadan, South West of Nigeria. 200 case notes of hypertensive patients attending the hypertension clinic during the study period were

randomly selected. The case notes were screened and relevant data extracted using a pre-piloted data collection form. The information collected were patient's hospital number, age, gender, hypertension diagnosis, co-existing diseases, average blood pressure reading at first attendance at the clinic and last average blood pressure reading as at the time of study, current anti-hypertensive drugs prescribed including dose, frequency of dosing, anti-hypertensive drugs combination, documented level of patients' adherence, as assessed by physician interviews/patients' self-report during consultations and adverse reactions documented by physicians in patients' chart. All cases where patients were documented by physicians as using their prescribed anti-hypertensive drugs regularly since last clinic visit were defined as adequate adherence, while those who did not were rated as inadequate.

The diagnosis of mild, moderate, severe and systolic hypertension was based on WHO- ISH (1999) Guideline (1). The appropriateness of dose; regimen and possibility of occurrence of potentially harmful drug interactions were done using relevant references (30). The office of the Chairman, Medical Advisory Committee, granted formal approval for the study and strict confidentiality was assured. Data analysis was carried out with descriptive statistics.

RESULTS

Out of the randomly selected 200 case notes of hypertensive patients, 11 were discarded for incompleteness. 73% (138) of the cohort were on anti-hypertensive drug combinations while 27% (51) were on monotherapy. 34.8% (48) of the cohort on combination therapy were males while 65.2% (90) were females with mean age of 57years. Severe hypertension appears most prevalent (34.1%) followed by moderate hypertension (29%), mild hypertension (27.5%) and systolic hypertension (9.4%). Type-2 diabetes mellitus was the most frequent co-morbidity among hypertensive patients on combination therapy (32.7%), followed by osteoarthritis (21.8%), congestive heart failure (9.1%), peptic ulcer (7.3%), chronic renal failure (7.3%). Cataract, left ventricular hypertrophy, hypertensive retinopathy and prostatic hypertrophy had prevalence of 5.5% each.

Table 1: Pattern of prescribed anti-hypertensive drug combinations

	n=138	%
2-drug combinations		
C + D	40	29
A + C	11	8
A + D	9	6.5
B + D	1	0.7
Methyldopa + D	26	18.8
Methyldopa + C	4	2.9
Methyldopa + A	1	0.7
Brinerdin® + A	4	2.9
Brinerdin® + D	3	2.2
3-drug combinations		
Methyldopa + C + D	21	15.2
B + C + D	3	2.2
Methyldopa + A + C	2	1.4
Methyldopa + Brinerdin® + D	2	1.4
Brinerdin® + C + D	2	1.4
Methyldopa + A + D	2	1.4
Methyldopa + C + B	1	0.7
Methyldopa + B + D	1	0.7
4-drug combinations		
Methyldopa + B + C + D	4	2.9
Methyldopa + A + C + D	1	0.7

A : Angiotensin Converting enzyme inhibitors, B : Beta-blockers, C : Calcium channel blockers, D : Diuretics. Brinerdin® contains Reserpine, Dihydroergocristine and Clopamide

Overall, our study shows that 71.7% (99) of cohort were on 2-drug combinations, 24.4% (34) on 3-drug combinations and 3.6% (5) on 4-drug combinations. The pattern of prescribed anti-hypertensive combinations is as shown in Table 1. Thiazide diuretic, consisting mainly of fixed dose combination of Amiloride and Hydrochlorothiazide (Moduretic®) was the most frequently prescribed drug class used in combinations with other anti-hypertensives. ACE inhibitor, Lisinopril (Zestril®), was prescribed in combination with Moduretic®, Calcium channel blocker and beta-blocker in 6.5%, 8.5% and 0.7% respectively. Blood pressure control was adequate in only 29% (40).

Patient adherence with therapy was documented as adequate in 77.5% (107) of cohort. The prevalence of potentially harmful drug-drug interactions was 17.5%. These include lisinopril + amiloride/hydrochlorothiazide (51.5%) and aspirin + NSAIDs (48.5%).

Finally, adverse drug reactions were documented, by physicians, in only 10.9% (15) of cohort. Dizziness, drowsiness, insomnia and nightmares, attributed to methyldopa and Brinerdin®, accounted for 46.7% (7) of documentation, followed by gastritis, 33.3% (5), due to aspirin + NSAIDs and severe headache, 20% (3), due to nifedipine. However, there appear to be

currently no organized institutional adverse drug reaction monitoring, detection and documentation system in place. Documentation is left at the physicians' discretion.

DISCUSSION

Our findings that 73% of the hypertensive patients were on prescribed anti-hypertensive combination therapy is consistent with the recommendation of several studies which demonstrated that combination therapy was necessary in at least 70% of cohort to achieve optimal blood pressure control (1-5,17). This high usage rate appear to be due to the observed high prevalence of severe and moderate hypertension among patients, both of which accounted for 63.1% of hypertension diagnosis at the clinic and this is consistent with the established fact that black hypertensives, who incidentally tend to have higher co-morbidities of diabetes, left ventricular hypertrophy and heart failure, have increased risk of severe hypertension, morbidity and mortality due to cardiovascular and cerebrovascular events and end-organ damage (7-10). Therefore aggressive treatment to achieve sustained control of blood pressure through use of right combinations of anti-hypertensive drug appears to be the right therapeutic approach (5,12-14,31). However, we did not find that blood pressure control is adequate in the 73% of patients on combination therapy. Indeed blood pressure control was adequate in only 29% of the patients. Despite the consistency of this finding with the global trends in blood pressure control among hypertensive patients (32-34) and specifically with the findings of Akinkugbe O.O (2000) among Nigerian (35). The negative impact of inadequate blood pressure control on morbidity and mortality due to hypertension are well documented (36-39) and this is a possible contributory factor to the documented considerable morbidity and mortality due to severe and malignant hypertension among Nigerians.

Notwithstanding the use of combinations of anti-hypertensive drugs in 73% of patients, it is not readily clear why the degree of blood pressure control is at variance. Patient adherence, a critical factor for achieving good blood pressure control, was documented by physicians as adequate in 77.5% of cohort; yet blood pressure control remain inadequate

in majority of patients. These are conflicting findings, as the documented high patient adherence ought to have impacted positively on the observed level of blood pressure control. The possibility of insufficient investigation of patient adherence cannot be ruled out, as high patient self-report, for reason of desirability, could confound the documented level of adherence especially when it is not evident that patients' adherence level is being validated by other methods beside interview by physicians (40). Furthermore, the pervasiveness of counterfeit drugs in the poorly regulated drug distribution channels in Nigeria also poses a substantial threat to achievement of good blood pressure control among hypertensive patients as possible use of counterfeits anti-hypertensive drugs will impact negatively on patient outcomes (41-43). These are potential focus for subsequent study among hypertensives in Nigeria. Several studies have however identified some factors responsible for inadequate blood pressure control among Nigerian hypertensives and these includes late presentation for treatments often with possible onset of end-organ damage, delayed diagnosis and commencement of treatment, inadequacy of pharmacological treatment, non-adherence with prescribed anti-hypertensive regimen, low socio-economic/underprivileged class and subsequent inability to afford cost of drug prescribed and exposure to greater degree of stress (21,22,24-28). Successful management of hypertension requires a holistic approach involving the use of appropriate anti-hypertensives alone or in right combinations, the individualisation of therapy which consider patient's co-morbidities and other features in their lifestyles, the participation of patients, their family, physicians, pharmacists and nurses. The outcome of such intervention is influenced by treatment acceptance and subsequent adherence by patients; a product of patients' tolerability of the selected drug therapy, minimal disruption of their quality of life, accommodation of their concerns and expectations and attitude of physicians, pharmacists and nurses to these factors (1,3,5,44).

Notwithstanding the use of drug combination in 77.5% of hypertensive patients, only 15.2% were on combinations that appear beneficial and is consistent with recommendations of guidelines for anti-hypertensive combination therapy (8% on A+C, 6.5% ON A+D and 0.7% on B+D). The use of

combination of ACE inhibitors and diuretics or calcium channel blocker is particularly beneficial in black hypertensive patients because such combination have been shown to result in improved blood pressure control and reduction of end-organ damage, particularly cardio- and renoprotection (10-15,45). This combination was however prescribed in only 14.5% of hypertensive patients at our study setting. That the population of cohort on combinations which does not appear consistent quadrupled that of those on combinations that are consistent and appear beneficial underscores the need for institutionalized, local and national interventions to regularly appraise anti-hypertensive combination therapy; with a view to ensuring that only combinations which will be beneficial to patients are prescribed and used. This is more likely to contribute to positive treatment outcomes and reverse the considerable morbidity and mortality from malignant hypertension among Nigerian hypertensives. However, there was an attempt by the Nigerian Hypertension Society to produce such a guideline in 1996 but this was unsuccessful as the widespread application of such guideline appear limited and its impact remain to be seen (26,46). The AB/CD combinations recommended by several studies could serve as a useful guide in producing such standard guideline for anti-hypertensive combination therapy; as was done in a study by DiTusa et al 2001 (47) who reported that 68% of patients treated in a managed care setting in the United States of America were prescribed anti-hypertensive agents recommended by a locally developed guideline which was based on the sixth report of Joint National Committee on Prevention, Detection, Evaluation and Treatment of hypertension.

Our findings with regards to pattern of prescription of anti-hypertensive combinations is consistent with that of Adigun et al 2003 (48) who reported that Thiazide diuretic was the most frequently used drug class in anti-hypertensive combinations therapy (56%) in a similar study setting in Nigeria. We however observed an even higher frequency of usage (83.3%) (Table1). Our study also, in contrast with Adigun et al 2003, shows that fixed dose combination of Amiloride and Hydrochlorothiazide rather than hydrochlorothiazide alone, accounted for all the thiazide diuretic component of the anti-hypertensive combinations

used and this finding is consistent with that of Yusuff et al 2005 (49). This considerable use of thiazide diuretic is consistent with the findings of many studies which have documented their efficacy especially at carefully titrated doses, in black hypertensive (3,6,14). However, some studies have documented an even greater short and long term benefits when combination of thiazide diuretics and ACE inhibitors or Calcium channel blockers are used in high risk population, such as black hypertensives (7,12-14).

It is important to emphasize the considerable use of various anti-hypertensive combinations that were not only inconsistent with the subsisting international guidelines, but appear atypical of anti-hypertensive practices in other countries. Indeed, 55% of the cohorts on combination therapy were on these drug combinations which were mainly made up of methyldopa and amiloride / hydrochlorothiazide. Methyldopa's usage, alone or in combinations, has considerably reduced in the developed world due to their relatively less favourable side effects and their potential for causing positive Commb test in at least 20% of patients (1). Furthermore, central nervous system side effects, due to methyldopa, also accounted for the majority of documented adverse reactions in cohort studied (46.7%). The negative impact of patients' experience of adverse effects on level of adherence and subsequent outcome of therapy are well documented (50-51). These however does not appear to have significantly influence its rate of prescribing at our study site. Its considerable use appears driven mainly by economic considerations, as cheap generics abounds. While there may be nothing wrong with such consideration in a resource-limited setting like Nigeria, the probable disproportionate reliance on cost consideration and probable shift of focus from other important factors, such as possibility of non-adherence due to side effects and cumbersome dosage schedule, which might militate against successful outcome of anti-hypertensive therapy, appear to restrict access of patients to prescribing choices which are more likely to be beneficial (52-53). There is therefore a need for a shift of paradigm to identify cost-reduction strategies, which will not limit prescribing choices and restrict access to beneficial anti-hypertensive combinations. It is important to note the considerable use of 2-drug

combinations (71.7%) compared to 3-drugs and 4-drugs combinations, suggesting that physicians are probably cognizant of the negative impact of use of too many anti-hypertensive drug combinations which may increase possibility of occurrence side effects and reduce patient adherence to anti-hypertensive therapy.

The prevalence of potentially harmful drug interactions in patients on combination therapy was 17.5%. Ambulatory patients on combination of lisinopril and amiloride/ hydrochlorothiazide are particularly at risk of severe hyperkalemia, particularly when monitoring of serum potassium level is not evident. The use of aspirin with other NSAIDs in patients with co-morbidity of osteoarthritis need to be further carefully studied. This will ensure that patients are not at increased risk of upper gastrointestinal bleeding/perforation and inadequate blood pressure control due to the use of this combination.

The documentation of adverse drug reactions among hypertensive patients by physicians appear low (10.9%). This may be due to the non-availability of institutionalized and well-coordinated adverse drug reactions monitoring, detection and documentation system within Nigeria's health system; thereby leaving such documentation at the discretion of clinicians. This findings is similar to that of Adigun et al 2003 (48), who reported a frequency of 11% among hypertensives in a similar study setting. This is a clearly missed opportunity that may be useful in determining the frequency of occurrence of adverse reactions especially in patients on combination therapy with a view to identifying combinations which are impacting negatively on patients' adherence and safety. There is therefore a clear need for an institutionalized adverse drug reactions monitoring system, as this is more likely to contribute to positive outcome of anti-hypertensive drug therapy.

In conclusion, our study shows that the prescription of anti-hypertensive drug combinations among hypertensive patients in a tertiary care setting in southwestern Nigeria is considerable. However, this practice does not appear to have impacted positively on the overall blood pressure control

among patients and nor is It modulated by an institutionalised standard treatment guideline.

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