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Fixed-dose versus separate drug combinations for antihypertensive treatment: literature review

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Abstract

INTRODUCTION
Hypertension requires effective interventions to reduce cardiovascular morbidity and mortality. Drug therapies have achieved optimal blood pressure levels in affected patients. Recent clinical guidelines suggest drug combinations a fact that has led to the development of various fixed-dose combinations.

OBJECTIVE
To find the best available evidence about the effectiveness of antihypertensive drugs in fixed-dose combinations compared with separate dose combinations for blood pressure control, treatment adherence and reducing cardiovascular morbidity and mortality.

METHODS
Systematic literature search of the best evidence available in the following databases was performed: MEDLINE/PubMed, LILACS, Cochrane and institutional publications of WHO and PAHO.

RESULTS
Two meta-analyses comparing the two combinations were found, in both studies medication compliance was evaluated, no control of blood pressure or effects on cardiovascular events was assessed. Both studies are of very low quality of evidence due to limitations in search methodology, suboptimal quality of the included studies and heterogeneity of the analyzed variables. WHO drug use policies for antihypertensive drugs do not suggest fixed-drug combinations. These combinations are not included in Chile´s national drug formulary.

CONCLUSION
Well-designed studies are required to demonstrate the effectiveness of antihypertensive drugs in fixed-dose combination compared with separate dose combinations for controlling blood pressure, treatment adherence and reducing cardiovascular morbidity and mortality.

Introduction

Hypertension is a global and national public health problem; its treatment is mainly aimed to reduce associated cardiovascular morbidity and mortality. It is recommended to achieve optimal blood pressure readings, especially in young individuals and patients with cardiovascular disease, diabetes or kidney disease. The onset of antihypertensive drug treatment should be in accordance with baseline values and coexistence of other

cardiovascular risk factors and/or injury to the target organs. Guidelines from scientific societies recommend starting with a low dose of a single antihypertensive drug, or the combination of two agents. These guidelines also recommend a rational use of antihypertensive drugs choosing the ones that best suit the patient´s characteristics [1].

The rationale for recommending the combination of antihypertensive treatment in a high percentage of patients stems from the results of several clinical trials evaluating blood pressure control with the use of two or more drugs, including: Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) [2], Appropriate Blood Pressure Control in Diabetes Trial (ABCD) [3], Modification of Diet in Renal Disease Study (MDRD) [4] and Hypertension Optimal Treatment Study (HOT) [5]. However, it has also been mentioned that separate dose combinations entail problems in treatment compliance, due to greater complexity in its administration. For this reason, an increasingly number of drugs with fixed-dose combinations (FDCs) have emerged for the treatment of hypertension. More recently, fixed dose combination of antihypertensive drugs with other drugs such as statins and antiplatelet agents for simultaneous control of other cardiovascular risk factors have appeared based on their demonstrated greater adherence. However, the effects of these therapies on the occurrence of cardiovascular events are still uncertain [6],[7].

Concomitant use of two or more drugs cmplicates individual adjustment of pharmacotherapy. It is important to tailor the dose of each drug to achieve optimal benefit. In this respect patient compliance is essential, although it is more difficult to achieve. To face the latter problem, fixed-dose combinations of drugs are available in the market. Their use would be advantageous if the proportion of fixed dose correspond to the needs of each patient [8].

Many countries have authorized the marketing of these products and there are no requirements, under the regulations of each country, for supporting studies to have the highest quality of evidence from the methodological point of view. Many agencies show flexibility for the approval of these drugs. So, many products are approved based on the results of rigorous studies but others are approved on the basis of less severe ones. This means there are different levels of certainty about the benefits and risks of medicines approved, thus it necessary to continue evaluating them in the post market phase [9].
Instead, the best quality of evidence must be required if it is considered to include them within national drug formularies to be financed by the public health system. Hence the interest in evaluating the best literature evidence on the effectiveness of drugs in fixed-dose combinations compared with separate doses for controlling blood pressure, treatment adherence and cardiovascular morbidity and mortality reduction. All this for an eventual suggestion about their introduction in national drug formularies.

Objective

To identify the best literature available evidence on the effectiveness of antihypertensive drugs in fixed-dose combination compared with separate dose combinations for controlling blood pressure, treatment adherence and reducing cardiovascular morbidity and mortality.

Methods

A literature search in the following databases was performed: MEDLINE/PubMed, LILACS, Cochrane and institutional publications of WHO and PAHO. Other databases were not consulted due to lack of access. Key words were: "antihypertensive agents", "fixed-dose combination" with the filters: meta-analysis, systematic review and controlled clinical trials published until June 2016, without language, geographic or time restrictions. In the database of PAHO-WHO publications about drug Policy and adherence were obtained. We excluded studies not comparing the two therapeutic schemes or comparing schemes with combined fixed-dose drugs but not antihypertensive agents.

Each study was analyzed individually and independently by the researchers in terms of its internal validity and according to design. The PRISMA statement was considered for systematic reviews and/or meta-analysis. For clinical trials we examined: design, method, allocation concealment, loss to follow up and we used the Jadad scale.

Results

From the search with keywords in MEDLINE/PubMed 481 studies were obtained. After the application of the methodological filters described, eleven studies were left and of these: only two met the inclusion criteria. These studies corresponded to two meta-analyses, no clinical trials were found. The search of Cochrane and LILACS did not return new results. In addition, two official WHO documents were reported on this issue.

The first study is a meta-analysis that assesses compliance with antihypertensive drug treatment with fixed-dose combination comparing vs separate combination of drugs [10]. In this study the database search is limited to MEDLINE/PubMed and English language. A total of nine included studies evaluating various pathologies: two for Tuberculosis, one for HIV, four for Hypertension and two for Diabetes. Studies for HIV and Tuberculosis were randomized clinical trials and for blood pressure and diabetes were retrospective analysis of data from the pharmaceutical industry. There is no critical report of included studies of hypertension and diabetes and no adjustment for variables that can cause confusion implying biases in the results. Variables included were age, degree of hypertension, socioeconomic status, and others (related to non-compliance). Two studies show no accurate results.

Regarding outcome measures, in studies of hypertension and diabetes the primary and clinically relevant efficacy (control of blood pressure or diabetes) was not evaluated. They report that adherence is evaluated, but the variable

actually measured is possession of drugs. The authors conclude that combined fixed-doses reduce the risk of non-compliance and their use should be considered in chronic conditions as hypertension to achieve better clinical outcomes.

The second study is a meta-analysis assessing compliance, safety and effectiveness of antihypertensive drug treatment comparing combined fixed-doses vs separate doses drugs [11]. The search conducted is wider (MEDLINE/PubMed, Cochrane, Web of Science and manual search), limited to English language. Fifteen studies were included, nine were uncontrolled clinical trials and six retrospective studies. That is to say, studies of suboptimal quality.

In this meta-analysis, a critical evaluation of the studies is performed and it is described that in some studies drug classes rather than a specific drugs are evaluated. Furthermore, it describes that there are confounders like the presence of co-morbidities and concomitant medications, but adjustment cannot be made in view of the study design and the limited power of the studies.

Regarding outcome measures, definitions for their evaluation are heterogeneous, unclear and insufficient, particularly in the assessment of compliance and measuring blood pressure to evaluate antihypertensive efficacy. Protocol evaluation is performed. Finally, the authors conclude that combined fixed-doses of antihypertensives increases compliance and that trends of no significant improvement in blood pressure and adverse effects are reported.

Discussion

The two studies reported represent the best information available, based on evidence: meta-analyses on the subject of antihypertensive drugs in fixed-dose combination compared with separate combination. The majority of published studies refer to comparisons between fixed-dose combination and separate monotherapies or comparisons between two fixed-dose combinations and therefore were excluded. The quality of evidence of the studies described, which are those that met the requirements of the search are of very low quality of evidence. The studies included in these meta-analyses are of suboptimal quality since they include retrospective data. Therefore, results which describe that medication with fixed-dose combination improves treatment compliance may be substantially different from the actual effect.

Additionally the studies found do not evaluate relevant clinical variables, such as blood pressure control and/or morbidity and mortality from cardiovascular events. It is not possible to conclude about the effectiveness of fixed-dose combination antihypertensives on this effect.

With regard to achieving compliance with the treatment, referred to in the studies found, this is not an interchangeable term with adherence to treatment. And still less is to infer that compliance leads to pressure control and other cardiovascular outcomes. Adherence to treatment has five large dimensions to be addressed: social and economic (income, presence of networks); related to the health system (coordination, comprehensiveness); the related pathologies (asymptomatic chronic, acute, etcetera); the patient-related statement (motivation) and of course the one related to treatment (complexity, dosing). To address the adherence from only one perspective reduces the view of the analysis and therefore the conclusions.

WHO in its official publication on adherence to long-term treatments, specifically in the chapter of hypertension and therapeutic dimension, suggested the simplification of procedures as an effective intervention. This is a different strategy than to provide antihypertensives with fixed-dose combination [12].

Similarly, WHO, in its issues on drug policy and development of essential drugs or therapeutic forms, does not incorporate the fixed-dose combination in hypertension as a policy. Among fixed-dose combination drugs accepted for scientific validity and supported clinical experience are: beta-lactams plus beta-lactamase inhibitors, oral contraceptives, HIV and tuberculosis [13].

In Chile, there are approximately 16,000 registered products, and it is estimated that approximately 8,000 are marketed within which few are fixed-dose combinations. In the National Drug Formulary for use in public health institutions, in the cardiovascular drug group, fixed dose combinations are not described.

The guidelines of drug policy in Chile enacts the drug as a primary social good, and guarantees access, availability, quality, safety, efficacy and affordability of medicines, along with their rational use [14]. Still, Chile is one of the countries with the highest pocket-spending in medicines as an important source of funding[15]. Although there is a disaggregated system that assigns health facilities the freedom to choose between direct or centralized purchases, these must be based on real therapeutic needs and drugs which demonstrate safety, quality, effectiveness and efficiency. They must not obey to professional pressures influenced by a pharmaceutical market with information asymmetry but make the right decision for the benefit of the collective.

Conclusion

Well-designed studies to demonstrate the effectiveness of antihypertensive drugs in fixed-dose combination compared with separate dose combinations for controlling blood pressure, treatment adherence and reduce cardiovascular morbidity and mortality are required.

Study limitations: search in other databases due to lack of access and inclusion of safety assessment and adverse effects.

Notes

From the editor
The authors originally submitted this article in Spanish and subsequently translated it into English. The*Journal* has not copyedited this version.

Conflicts of interest
The authors completed the ICMJE conflict of interest declaration form, translated to Spanish by *Medwave*, and declare not having received funding for the preparation of this report, not having any financial relationships with organizations that could have interests in the published article in the last three years, and not having other relations or activities that might influence the article´s content. Forms can be requested to the responsible author or the editorial direction of the *Journal*.

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