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[Intervention Review]

Eplerenone for hypertension

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ABSTRACT

Background

Eplerenone is an aldosterone receptor blocker that is chemically derived from spironolactone. In Canada, it is indicated for use as adjunctive therapy to reduce mortality for heart failure patients with New York Heart Association (NYHA) class II systolic chronic heart failure and left ventricular systolic dysfunction. It is also used as adjunctive therapy for patients with heart failure following myocardial infarction. Additionally, it is indicated for the treatment of mild and moderate essential hypertension for patients who cannot be treated adequately with other agents. It is important to determine the clinical impact of all antihypertensive medications, including aldosterone antagonists, to support their continued use in essential hypertension. No previous systematic reviews have evaluated the effect of eplerenone on cardiovascular morbidity, mortality, and magnitude of blood pressure lowering in patients with hypertension.

Objectives

To assess the effects of eplerenone monotherapy versus placebo for primary hypertension in adults. Outcomes of interest were all-cause mortality, cardiovascular events (fatal or non-fatal myocardial infarction), cerebrovascular events (fatal or non fatal strokes), adverse events or withdrawals due to adverse events, and systolic and diastolic blood pressure.

Search methods

We searched the Cochrane Hypertension Specialised Register, CENTRAL, MEDLINE, Embase, and two trials registers up to 3 March 2016. We handsearched references from retrieved studies to identify any studies missed in the initial search. We also searched for unpublished data by contacting the corresponding authors of the included studies and pharmaceutical companies involved in conducting studies on eplerenone monotherapy in primary hypertension. The search had no language restrictions.

Selection criteria

We selected randomized placebo-controlled trials studying adult patients with primary hypertension. We excluded studies in people with secondary or gestational hypertension and studies where participants were receiving multiple antihypertensives.

Data collection and analysis

Three review authors independently reviewed the search results for studies meeting our criteria. Three review authors independently extracted data and assessed trial quality using a standardized data extraction form. A fourth independent review author resolved discrepancies or disagreements. We performed data extraction and synthesis using a standardized format on Covidence. We conducted data analysis using Review Manager 5.



Main results

A total of 1437 adult patients participated in the five randomized parallel group studies, with treatment durations ranging from 8 to 16 weeks. The daily doses of eplerenone ranged from 25 mg to 400 mg daily. Meta-analysis of these studies showed a reduction in systolic blood pressure of 9.21 mmHg (95% CI -11.08 to -7.34; I² = 58%) and a reduction of diastolic pressure of 4.18 mmHg (95% CI -5.03 to -3.33; I² = 0%) (moderate quality evidence).

There may be a dose response effect for eplerenone in the reduction in systolic blood pressure at doses of 400 mg/day. However, this finding is uncertain, as it is based on a single included study with low quality evidence. Overall there does not appear to be a clinically important dose response in lowering systolic or diastolic blood pressure at eplerenone doses of 50 mg to 400 mg daily. There did not appear to be any differences in the number of patients who withdrew due to adverse events or the number of patients with at least one adverse event in the eplerenone group compared to placebo. However, only three of the five included studies reported adverse events. Most of the included studies were of moderate quality, as we judged multiple domains as being at unclear risk in the 'Risk of bias' assessment.

Authors' conclusions

Eplerenone 50 to 200 mg/day lowers blood pressure in people with primary hypertension by 9.21 mmHg systolic and 4.18 mmHg diastolic compared to placebo, with no difference of effect between doses of 50 mg/day to 200 mg/day. A dose of 25 mg/day did not produce a statistically significant reduction in systolic or diastolic blood pressure and there is insufficient evidence for doses above 200 mg/day. There is currently no available evidence to determine the effect of eplerenone on clinically meaningful outcomes such as mortality or morbidity in hypertensive patients. The evidence available on side effects is insufficient and of low quality, which makes it impossible to draw conclusions about potential harm associated with eplerenone treatment in hypertensive patients.

PLAIN LANGUAGE SUMMARY

Eplerenone for high blood pressure

Review question

The aim of this review was to determine the effectiveness of eplerenone for reducing blood pressure, its side effect profile, and its impact on clinically meaningful outcomes such as mortality and morbidity.

Background

Clinicians have used eplerenone to treat high blood pressure since 2002. It is important to determine the clinical impact of all antihypertensive medications used in patients to support their continued use in essential hypertension. We searched multiple databases and found five eligible studies in 1437 people who received either eplerenone or no medication in a random fashion.

Study characteristics

The doses of eplerenone used in these studies ranged from 25 mg to 400 mg daily. These studies followed patients for 8 to 16 weeks while on therapy. None of the studies reported on the clinically meaningful outcomes of eplerenone, such as whether eplerenone can reduce heart attacks, stroke, or death compared to placebo. Only three of the five studies reported on side effects.

Key results

There is currently no evidence that eplerenone has a beneficial effect on life expectancy or complications rleated to hypertension (e.g. heart attack, stroke). Evidence for risk of side effects with eplerenone is limited and of poor quality; it is difficult to tell the extent of possible harm with eplerenone versus placebo. This meta-analysis shows that eplerenone 50 to 200 mg/day reduces systolic blood pressure by approximately 9 mmHg and diastolic blood pressure by 4 mmHg compared to taking no medication.

Quality of the evidence

We judged the five included trials to be of moderate quality, as authors did not extensively describe portions of their methodology.