# Eplerenone

*G Marshall*, G McKay, M Fisher*

## Introduction

Aldosterone acts principally on the collecting tubules of the kidney to regulate sodium and water homeostasis. Aldosterone also acts directly on other tissues including the vasculature and heart, where it may contribute to tissue fibrosis, pathological cardiac remodelling and endothelial dysfunction. Excessive aldosterone production or excessive neurohumoral activation, as seen in heart failure, may contribute directly to both the disease processes and resulting end-organ damage. Blockade of aldosterone in these settings is therefore an attractive therapeutic target.

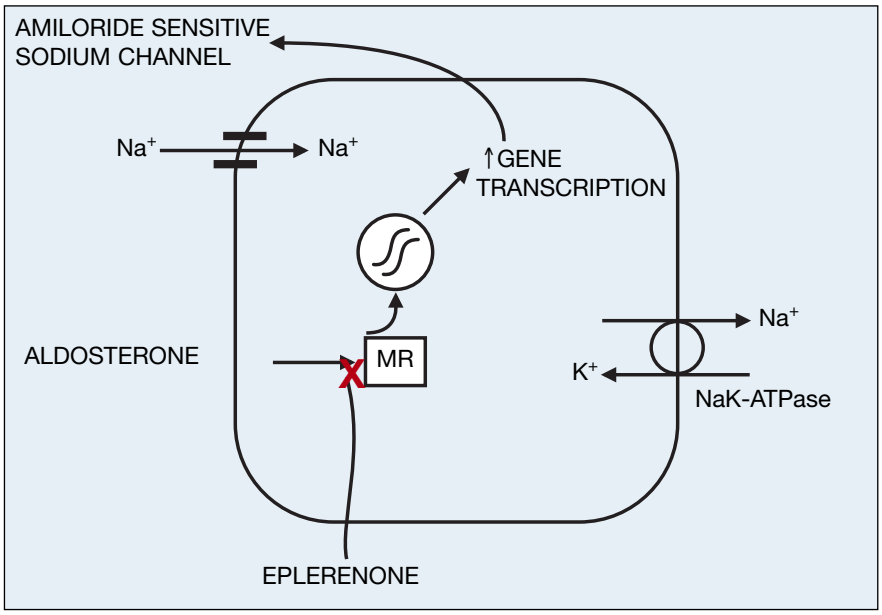
## Pharmacology

Figure 1 outlines the pharmacological action of eplerenone. Aldosterone acts by binding to the intracellular mineralocorticoid receptor (MR) which translocates to the nucleus and induces transcription of a variety of genes. Within the collecting tubules of the kidney this results in the expression of the amiloride-sensitive sodium channel and NaK-ATPase, leading to increased sodium and water retention with excretion of potassium, promoting expansion of intravascular volume and increased blood pressure.

Eplerenone is the first specific MR antagonist and was derived from spironolactone, the other widely used but non-specific MR antagonist. Eplerenone has a reduced affinity for progesterone and androgen receptors, minimising side effects of gynaecomastia, mastodynia and menstrual irregularities associated with spironolactone. It has a shorter elimination half-life than spironolactone, due to breakdown into inactive metabolites. It is approximately 50% protein bound in plasma and is metabolised by a variant of the enzyme cytochrome P450 within the liver. Consequently, eplerenone has the potential to interact with drugs that inhibit this enzyme, including the azole antifungals and macrolide antibiotics, and its pharmacokinetics are altered in significant liver impairment.

The main adverse side effect of eplerenone is hyperkalaemia which is directly related to its mechanism of action within the kidneys. The increase in serum potassium is dose dependent and is also affected by the presence of impaired renal function, and concomitant use of ACE inhibitors and potassium-sparing diuretics. Its use is contraindicated when the serum potassium is >5.5mmol/L and should be avoided if creatinine clearance is <50ml/min.

**Figure 1.** Pharmacological action of eplerenone, a specific mineralocorticoid receptor (MR) antagonist, in the collecting tubules of the kidney




## Trials of safety and efficacy

### *Hypertension*

A number of studies examined the safety and efficacy of eplerenone in the treatment of essential hypertension both as monotherapy and in combination with other antihypertensives. The 4E study was a double-blind randomised study of 200 patients with hypertension and left ventricular (LV) hypertrophy who were treated with eplerenone, enalapril or a combination of both with the addition of further diuretic or calcium channel blocker if blood pressure remained elevated after eight weeks.[1] After nine months of treatment, high-dose eplerenone (200mg) was as similarly effective as high-dose enalapril (40mg) at reducing blood pressure and LV mass but less effective than the combination of the two drugs (10mg enalapril and 200mg eplerenone), although

**Gillian Marshall,** PhD, MRCP, Cardiology Specialist Registrar
**Gerry McKay,** BSc (Hons), FRCP, Consultant Physician
**Miles Fisher,** MD, FRCP, Consultant Physician
Medical Directorate, Glasgow Royal Infirmary, Glasgow, UK

***Correspondence to:** Dr Gillian Marshall, Cardiology Department, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK; e-mail: marshall@clinmed.gla.ac.uk

direct comparison between the efficacy of the treatment groups was complicated by the differing rates of add-on antihypertensive drugs.

### *Heart failure*

The efficacy of eplerenone in acute heart failure post-myocardial infarction was studied in the large randomised double-blinded EPHESUS trial.[2] In all, 6642 patients were randomised within three to 14 days of an acute myocardial infarction to receive either eplerenone (25mg uptitrated to 50mg) or placebo in addition to standard best medical therapy. All patients had to have documented LV systolic dysfunction and clinical evidence of heart failure. After a mean follow up of 16 months there was a significant 15% relative reduction in the primary endpoint of all-cause mortality (CI 0.75–0.96, p=0.008) and a 13% relative reduction in the other primary endpoint of cardiovascular mortality or hospitalisation due to cardiovascular event (CI 0.79–0.96, p=0.002). Interestingly, and possibly related to beneficial effects on fibrosis, cardiac remodelling and arrhythmias, the incidence of sudden cardiac death in EPHESUS was significantly lower in the treatment group (RRR 0.21, CI 0.64–0.97, p=0.03). The rate of serious hyperkalaemia was higher in the treatment group, especially in those with a reduced creatinine clearance of <50ml/min at baseline.

It has been argued that the timescale of randomisation of patients in EPHESUS may have allowed for patients with transient LV dysfunction and clinical heart failure to be recruited, thus making it more of a post-myocardial infarction than a heart failure trial. Currently, there are ongoing trials examining the role of eplerenone in chronic heart failure.

## Specific evidence for use in diabetes

Many of the initial blood pressure trials of eplerenone excluded patients with diabetes. The efficacy of eplerenone as add-on therapy in diabetic nephropathy was evaluated in a randomised, double-blinded trial of 268 patients with type 2 diabetes using enalapril 20mg with either placebo, or with 50mg or 100mg of eplerenone.[3] Patients had $HbA_{1c}$ of ≤8.5%, urinary albumin:creatinine ratios (UACRs) of >50mg/g, serum potassium of <5.0mmol/L and reasonably well-controlled, although not optimal, mean blood pressures at around 140/80mmHg. After 12 weeks, there was a significant and similar reduction in blood pressure in all three treatment groups. Those treated with enalapril and eplerenone had a significant 7.4% reduction in UACR (p<0.001). The rates of hyperkalaemia were low with no significant differences between treatment groups, although this may partially reflect the low adverse event rates and small patient numbers in each group.

In EPHESUS, the largest study of eplerenone in patients with cardiovascular disease, almost one-third of patients had diabetes.[2] It should be noted that diabetes patients differed from the other patients recruited in that they did not need to have clinical evidence of heart failure but simply documented measurement of LV dysfunction prior to randomisation. Arguably, the diabetes patients in this trial may have had smaller infarcts and potentially less severe and/or sustained LV dysfunction than the non-diabetes patients, making this trial even more about post-myocardial management than heart failure within this population of patients. *Post-hoc* subgroup analysis of diabetes patients showed a significant 17% relative risk reduction (CI 0.71–0.98, p=0.03) in the combined endpoint of cardiovascular mortality and hospitalisation but not in all-cause mortality or sudden cardiac death, although the study was not powered to examine this. Within the diabetes subgroup there was a small but significant increase in the number of patients with hyperkalaemia (5.6 *vs* 3.0% of patients, p=0.015) which was similar to that in the whole treatment group.

## Conclusions

Eplerenone is an effective antihypertensive but is not licensed in the UK for this indication. It may have a future role to play in the management of diabetic nephropathy but more studies are needed. Eplerenone does appear to be effective in the treatment of patients, including those with diabetes, who have LV dysfunction and/or clinical heart failure after acute myocardial infarction but its role in the management of chronic heart failure is unclear. While a number of studies have provided evidence to support a good safety profile for this drug, many of these studies were small and restrictive. It may be that the incidence of serious hyperkalaemia in the real world setting will be greater than that reported in clinical trials.

### Key points

- Eplerenone is a specific mineralocorticoid receptor antagonist derived from spironolactone
- In a large study of patients with acute heart failure following myocardial infarction, including a significant proportion with diabetes, eplerenone reduced total mortality and hospitalisation due to cardiovascular events
- The effects of eplerenone in chronic heart failure are currently under investigation

## Conflict of interest statement

Dr Marshall and Dr McKay have no conflicts of interest to declare. Dr Fisher has received lecture fees from and has served on advisory boards for Pfizer.

## References

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