Eplerenone: A New Aldosterone Receptor Antagonist—Are the FDA's Restrictions Appropriate?

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Eplerenone is a new aldosterone receptor antagonist that will be used in the treatment of hypertension. Like spironolactone, it is a compound that can be associated with the development of hyperkalemia. Therefore, the same prescription considerations that are applied to spironolactone should be directed to its use. Unfortunately, the label for eplerenone will place more stringent restrictions on its use than is the case for spironolactone. The basis for the multiple contraindications to the use of eplerenone is primarily that of concern for the development of hyperkalemia. This may occur with eplerenone, as has been the case with spironolactone. The presumption in the prescribing information that certain patient subsets, such as diabetics with microalbuminuria and/or patients with mild renal failure, would be highly prone to developing clinically relevant hyperkalemia with eplerenone is not, however, grounded in fact. The favorable experience with spironolactone is important. It should provide us with the landmarks for advancing knowledge on the role of newer aldosterone receptor antagonists in disease state management and, one would think, help in establishing criteria for the safe use of new compounds. New compounds in a drug class typically provide advantages over earlier entries into a drug class but not if regressive labeling has occurred. Time and additional clinical experience with eplerenone will establish its safety profile and determine if the original label for this compound was correct. (J Clin Hypertens. 2002;5:441–445)
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Aldosterone, an effector hormone of the renin-angiotensin-aldosterone system, is increasingly viewed as playing an important role in both the development and progression of cardiovascular disease.[1–3] Historically, the role of aldosterone was believed to be played out almost entirely in the kidney. To this end, there is a wealth of pathophysiologic data describing the role of aldosterone in the kidney. For the most part, aldosterone was viewed as a "volume" hormone produced by zona glomerulosa cells in the adrenal gland. When aldosterone acted on epithelial tissue in the kidney and/or colon, sodium was retained and potassium and magnesium lost; thus, the well recognized state of hypokalemia that accompanied either states of primary or secondary hyperaldosteronism.

Knowledge now exists confirming that aldosterone production and action occur in other nonepithelial tissues including the brain, heart, and blood vessels where it can actively contribute to cardiovascular diseases such as hypertension, stroke, malignant nephrosclerosis, cardiac fibrosis, ventricular hypertrophy, and myocardial necrosis.[4] In turn, blockade of its actions in these nonepithelial tissues with an aldosterone receptor antagonist has been shown to provide meaningful experimental end-organ protection.[5]

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ALDOSTERONE RECEPTOR ANTAGONISTS

Spironolactone

Spironolactone was the first aldosterone receptor antagonist introduced into the US market. The process of its entry was an interesting one. Spironolactone underwent a series of approvals, withdrawals, and resubmissions during the years 1960 (100 mg strength), 1961 (100 mg strength), 1962 (25 mg strength), 1964 (25 mg strength), 1966 (25 mg strength), and 1981 (100 mg strength) before a final approval was granted on December 30, 1982 for marketing of the 50 mg strength. Spironolactone as the branded product (Aldactone) was released shortly thereafter. In the early 1980s several generic versions of spironolactone were approved even as the Aldactone product was being released. The fixed-dose combination of hydrochlorothiazide/spironolactone (50 mg/50 mg) (Aldactazide) was also approved on December 30, 1982.[6]

Aldosterone receptor antagonism effectively treats a number of disease states characterized by either primary or secondary increases in aldosterone. Most such conditions are distinguished by the presence of hypertension.[7–13] Aldosterone receptor antagonism with spironolactone has also proved useful in the treatment of refractory hypertension, which otherwise was not responsive to two or more antihypertensive medications.[14] The basis for such an antihypertensive effect is only now beginning to emerge. For example, it has been shown by Schohn et al.[15] that doses of spironolactone as low as 25 mg/d exert a marked inhibitory effect on cardiovascular reactivity to both the adrenergic and the renin-angiotensin systems.[15] The inhibitory effect achieved with spironolactone seems to be more durable than that seen with angiotensin-converting enzyme (ACE) inhibitors. Staessen et al.[16] showed that in patients receiving high doses of captopril (300 mg/d), plasma aldosterone levels were more than twice baseline values 12-months after having begun therapy. Thus, tachyphylaxis or an escape from inhibition of the renin-angiotensin-aldosterone system may occur after long-term treatment with an ACE inhibitor, a phenomenon that has not been observed with spironolactone.

Eplerenone

Widespread use of spironolactone has been limited because of progestational and antiandrogenic side effects, which arise from its binding to other steroid receptors. Gynecomastia, impotence, and menstrual irregularities have been most prominent among these side effects. For these reasons, aldosterone receptor antagonists with a higher affinity for the mineralocorticoid receptor and less activity at the androgenic and progestational receptors are under development. Eplerenone—the first agent of a new class of drugs known as the selective aldosterone receptor antagonists—is the most developed of the compounds in this class. A new drug application was accepted by the Food and Drug Administration (FDA) in January 2002; the FDA formally approved eplerenone in the latter part of September 2002. In early clinical trials eplerenone has proved to be a well-tolerated and effective antihypertensive medication either as monotherapy or as add-on therapy to any of a number of antihypertensive compounds.[17–19]

PACKAGE INSERT

Eplerenone

Eplerenone (Inspra) will be released in the near future. However, its label or package insert may prove confusing to many physicians. The following comments will hopefully clarify some of the issues surrounding the use of this compound. The product label, or package insert, is the 'manual' for the safe and effective use of a drug. Important pharmacokinetic and pharmacodynamic properties of a drug product typically appear in the label under specific sections, as required in the Code of Federal Regulations (CFR), using a format and language recommended by the FDA and provided in various guidances to the industry.[20] Also included on the label is important prescription information describing dose-related efficacy as well as relative and/or absolute contraindications to the use of a compound[21,22]; the latter can be provided in the form of a precautionary statement or as a black box warning in the package insert.[23] According to the federal regulations,[20] special problems, particularly those that may lead to death or serious injury, may be required by the FDA to be placed in a prominently displayed box. The boxed warning ordinarily should be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.[23]

The confusion with the eplerenone label will most likely arise on two accounts: first, physicians will find that warnings directed toward the use of eplerenone do not similarly appear in the most current label for spironolactone, a drug in the same class; second, if the prescription guidelines provided in the label are literally interpreted it will preclude important subsets of patients from receiving this compound. Importantly, competitive marketing by pharmaceutical companies will further complicate the use of this compound since the negatives of the compound will inevitably be stressed in a manner which is out of context. Finally, any issues of contraindication (or careful use) relating

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to eplerenone or for that matter spironolactone have little to do with molecule-specific toxicology; rather, they relate to an extension of the pharmacologic action of the compound and the likelihood of clinically relevant increases in serum potassium.

To lend some perspective to this issue, issues of relevance should be identified and discussed in the context of prescription use of eplerenone. Spironolactone has been available for two decades as a branded product (Aldactone) and has been available for some time in a generic form. The Aldactone version of spironolactone is no longer promoted and there no longer exists any commentary concerning it in the *Physician's Desk Reference* (*PDR*). The last reference to spironolactone, which might provide commentary on precautions to its use, can be found in the 2000 *PDR*, which is the basis for the comments on spironolactone in the Table. Importantly, the last available label for spironolactone may not have kept pace with clinical experience, absent any significant motivation for label change. The comments on eplerenone are taken directly from the package insert that will be available when this product reaches the market.

Contraindicated With a Serum Potassium of >5.5 mEq/L. This is a reasonable value for serum potassium above which eplerenone should not be started. However, potassium values this high are rarely seen in the general population; rather, they are found in patients with renal failure and, for that matter, in those with advanced renal failure in that the ability to maintain a "normal" serum potassium is preserved far into the renal failure process. Usually serum potassium values begin to rise at glomerular filtration rate values below 30 mL/min in nondiabetic renal failure patients. In the diabetic patient with renal failure, renal potassium handling is compromised at less advanced stages of renal disease, which mandates more careful use of these compounds in a diabetic population so afflicted.

However, the prevailing serum potassium value in any one patient is a product of multiple events. For example, diuretic therapy in a renal failure patient will often result in a reduction in serum potassium values and thereby establish a "concurrent therapy" dependent potassium baseline. With such a scenario in place aldosterone receptor antagonist therapy can still be considered in a renal failure patient, particularly if the potassium-sparing property of these compounds is a sought after attribute. Alternatively, in the case of concurrent therapy with either an ACE inhibitor or an angiotensin-receptor blocker, spironolactone and eplerenone should be prescribed with care since the effect on potassium retention can be significant with this combination.[24] Caution should be exercised with the coadministration of these drug classes whenever the serum potassium value exceeds 5 mEq/L.

Table. Comparison of the Package Labels for Spironolactone and Eplerenone

EPLERENONE	SPIRONOLACTONE
Contraindicated with a serum potassium of >5.5 mEq/L	Spironolactone is contraindicated in patients with hyperkalemia with no statement as to what qualifies as hyperkalemia.
Contraindicated in type 2 diabetes with microalbuminuria	No comment
Contraindicated with a serum creatinine of >2.0 mg/dL in men or 1.8 mg/dL in women	Spironolactone is contraindicated in patients with anuria, acute renal insufficiency, significant impairment of renal excretory function with no qualification as to the specific level of renal function where it would be contraindicated.
Contraindicated with a creatinine clearance of <50 mL/min	Spironolactone is contraindicated in patients with anuria, acute renal insufficiency, significant impairment of renal excretory function with no qualification as to the specific level of renal function where it would be contraindicated.
Contraindicated in patients treated concomitantly with potassium supplements or other potassium-sparing diuretics	The following is provided as a "Warning" but not a contraindication: potassium supplementation, either in the form of medication or a diet rich in potassium, should not ordinarily be given in association with spironolactone. Spironolactone should not be administered concurrently with other potassium-sparing diuretics.
Contraindicated with strong inhibitors of CYP450 3A4 such as ketoconazole or itraconazole	Not dependent on the CYP450 system for metabolism

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Contraindicated in Type 2 Diabetes With Microalbuminuria. The contraindication for use of eplerenone in type 2 diabetic patients with microalbuminuria is confusing. The presence of microalbuminuria per se should not restrict the use of this compound. In fact, eplerenone reduces urine albumin excretion comparable to what is seen with ACE inhibitors, and when given together with an ACE inhibitor, there is an additive antiproteinuric effect.[25] What this contraindication should have stated was that type 2 diabetic patients with microalbuminuria would more frequently develop hyperkalemia with eplerenone therapy; therein, lies the proviso for caution. Even absent this contraindication, the label already proposes criteria for potassium and level of renal function at which eplerenone is contraindicated. These potassium and level of renal function criteria should be applied here as well, which would allow this compound to still be given as adjunctive therapy for the treatment of microalbuminuria in the diabetic patient.

Contraindicated With a Serum Creatinine of >2.0 mg/dL in Men or 1.8 mg/dL in Women and Contraindicated With a Creatinine Clearance of <50 mL/min. The basis for contraindicating eplerenone with two different definitions of renal failure introduces additional confusion into the prescribing process. The presumption here is that a serum creatinine of >2.0 mg/dL in men or 1.8 mg/dL in women and a creatinine clearance of <50 mL/min are equivalent, which is not so. For instance, in a 60-year-old woman weighing 50 kg with a serum creatinine of 1.2 mg/dL, the calculated creatinine clearance is approximately 45 cc/min. This meets the contraindication criterion for creatinine clearance (<50 mL/min) but does not satisfy the contraindication criterion for serum creatinine. Quite logically, one would accept the lower of the two estimates for renal function and the drug by its label would now be contraindicated.

As currently written, this contraindication exists independent of the particular serum potassium values exhibited by a patient whether they are low, normal, or high. Contraindicating a compound by a specific level of renal function value sets a bad precedent, at least for this compound. Again, this compound should be contraindicated in the face of specific starting serum potassium values that are elevated and not on the basis of the level of renal function. The risk of hyperkalemia with eplerenone will increase as the level of renal function declines. However, this has also been the case for spironolactone, which has seen extensive use during the past two decades even in patients with reduced levels of renal function. In the case of spironolactone there was never a specific level of renal function at which its use was contraindicated; rather, it was left to the discretion of the prescribing physician. It is probably safe to presume that a physician's decision whether to use spironolactone or not was based on the likelihood of its resulting in a clinically dangerous elevation in serum potassium values. The same discretionary latitude for its prescription in renal disease should be provided for eplerenone.

Contraindicated in Patients Treated Concomitantly With Potassium Supplements or Other Potassium-Sparing Diuretics. This should be considered more of a "Warning" rather than a contraindication. It is not common practice to administer more than one potassium-sparing diuretic simultaneously; therefore, this is not really pertinent to the use of eplerenone. Alternatively, in patients with intolerance to potassium supplements and/or those exhibiting difficulty in correcting diuretic-related hypokalemia it is quite reasonable to combine a potassium-sparing diuretic with exogenous potassium supplementation to limit the amount of potassium that has to be taken. Moreover, all potassium-sparing diuretics are magnesium-sparing. Correcting the underlying magnesium deficiency in a diuretic-treated patient typically facilitates correction of potassium deficiency.[26]

If the label for eplerenone were interpreted in a literal fashion it would be contraindicated in diuretic-treated hypokalemic patients while such a patient might be able to receive triamterene, amiloride, and spironolactone, albeit with caution. Once again, having singled out one compound in a class for strong precautionary statements, as is the case for eplerenone, and not addressing the issues for the potassium-sparing drug class in a similarly forceful fashion, is unwise. *In one sense this contraindication lends itself to the interpretation that there is something "different" about eplerenone and that other compounds in this class can be used with a wider safety margin.* Although rigorous head-to-head studies among the various potassium-sparing diuretics have not been conducted, it is unlikely that upon review of the published literature, eplerenone, for example, would be a more potent potassium-sparing compound than might be spironolactone, which has a considerably longer tissue-based half-life.

Contraindicated With Strong Inhibitors of CYP450 3A4 Such as Ketoconazole or Itraconazole. Eplerenone is metabolized by the 3A4 isozyme of the CYP450 system; thus, when given with inhibitors of this system its blood levels will rise. When given together with potent inhibitors of CYP450 3A4 there is as much as a five-fold increase in the exposure to eplerenone. The consequences of such an increase in

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eplerenone are two. First, if concentration-related side effects exist they would occur with increased frequency. To date there have been no concentration-related side-effects described with eplerenone. Hence, based on a rise in the blood level of eplerenone alone there is not a specific justification for withholding therapy. Alternatively, in patients either at risk for the development of clinically relevant hyperkalemia or who are already hyperkalemic, there already exists the basis for not using eplerenone. It is in these patients, already prone to the development of hyperkalemia, that eplerenone should not be given with strong inhibitors of the CYP450 3A4 isozyme.

CONCLUSION

The final label for any new compound is arrived at through a series of careful negotiations between the FDA and the sponsoring company. This process generally works well. Consumer safety remains paramount in the process. Companies are compelled to abide by the label in how they market a compound. Sometimes though, as appears to be the case with eplerenone, the process does not achieve its goals. A byproduct of such failure is an unwieldy and internally inconsistent label, as has been the case with eplerenone. This in no way helps the prescribing physician and does not necessarily ensure greater patient safety. Resubmission of the eplerenone label can occur at some later date and one would hope that some of these inconsistencies could be rectified. Yet, until this occurs the prescribing physician will need to understand the origin of the concerns with this compound and the basis for the list of contraindications to its use.

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