



Hyperkalemia Due to Drug Interactions

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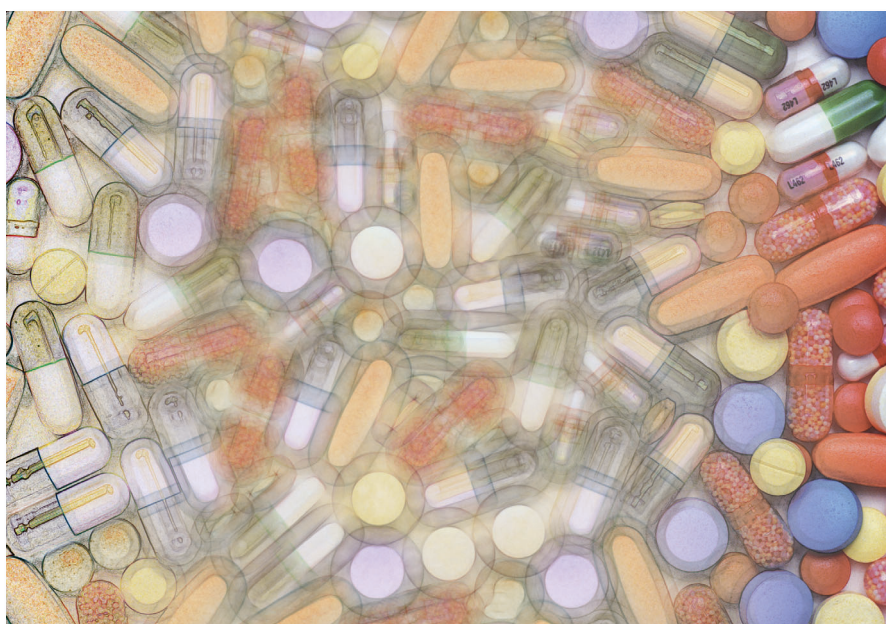
The most common drug interaction alerts in American pharmacies result from the concurrent prescription of various combinations of angiotensin-converting enzyme (ACE) inhibitors, potassium-sparing diuretics, and potassium supplements. These are difficult drug interaction alerts to handle, because the combinations are usually safe but occasionally result in life-threatening or fatal hyperkalemia. Therefore, it is important to identify patients in whom severe hyperkalemia is more likely to occur.

Why is this combination of drugs so common?

In 1999, the Randomized Aldactone Evaluation Study (RALES) showed that the addition of spironolactone to ACE inhibitors reduced morbidity and mortality in patients with moderate-to-severe heart failure.¹ In fact, the RALES study was terminated before completion because the results demonstrated a clear benefit. Subsequently, concurrent administration of ACE inhibitors and spironolactone has become commonplace.

Given the RALES results, what is the problem with giving spironolactone with ACE inhibitors?

In the RALES study, the risk of hyperkalemia was only 2% when spironolac-



tone was added to ACE inhibitors. This was not statistically different from the patients who received placebo instead of spironolactone, so the researchers naturally concluded that hyperkalemia was not a significant problem when spironolactone is combined with ACE inhibitors.

When the combination of spironolactone and ACE inhibitors began to be used in large numbers of patients, however, reports of severe (even fatal) hyperkalemia began to appear.²⁻⁵ As is so often the case, drugs used under carefully controlled conditions in a clinical trial were considerably safer than when the same drugs are used in the hectic world of actual medical practice. It is now clear that many patients who receive concurrent spironolactone and ACE inhibitors are

not receiving them appropriately and are at increased risk for hyperkalemia.

What factors appear to increase the risk of hyperkalemia?

Studies describing hyperkalemia due to concurrent use of spironolactone and ACE inhibitors have consistently revealed the same risk factors. Many of the patients who developed hyperkalemia had both diabetes mellitus and renal impairment. In some patients, the reduced renal function was secondary to other factors such as dehydration or worsening congestive heart failure.

Other characteristics common in patients who developed hyperkalemia with spironolactone plus ACE inhibitors included advanced age and concurrent use of other drugs that can increase serum potassium, such as potassium sup-

plements, nonsteroidal anti-inflammatory drugs or COX-2 inhibitors, trimethoprim, and nonselective beta-adrenergic blockers. Other drugs that may increase serum potassium concentrations include drospirenone, cyclosporine, tacrolimus, heparins, and pentamidine.

Using larger spironolactone doses also appears to increase the risk of hyperkalemia. Although the recommended spironolactone dose in the RALES trial was 25 mg/day, most of the patients who developed hyperkalemia, as described in subsequent reports, received spironolactone doses of 50 mg/day or more.

What about combining ACE inhibitors with other potassium-sparing diuretics?

ACE inhibitors combined with other potassium-sparing diuretics (eg, amiloride, eplerenone, triamterene) would also be expected to increase the risk of hyperkalemia. Indeed, life-threatening and fatal hyperkalemia have been reported with these combinations in predisposed patients.

It is also important to consider angiotensin II receptor blockers as similar to ACE inhibitors in that they both tend to increase the risk of hyperkalemia when combined with spironolactone or other potassium-sparing diuretics.

How can the risk of hyperkalemia from ACE inhibitors plus spironolactone be minimized?

- *Identify patients at risk.* Patients with diabetes and/or renal impairment are particularly at risk. Keep in mind that an acute reduction in renal function can occur following dehydration or worsening of heart failure. It is not clear whether advanced age is an independent risk factor, but many of the patients who developed severe hyperkalemia have been elderly.
- *Avoid excessive spironolactone doses.* Many of the patients who developed hyperkalemia received spironolactone doses of 50 to 100 mg daily, even though the recommended dose in the RALES study was 25 mg/day.
- *Use appropriate laboratory monitoring.* Serum potassium and renal function should be followed in patients on ACE inhibitors and spironolactone. This is especially important when the patient has one or more predisposing factors.

Conclusion

Although the combination of ACE inhibitors and spironolactone has been used safely in numerous patients, reports of life-threatening and even fatal hyperkalemia have appeared. In patients who are predisposed to hyperkalemia—especially if they have multiple risk factors—it is necessary to carefully weigh the benefit-risk of the combination. Patients should also be given the lowest effective dose of spironolactone, with appropriate monitoring of serum potassium and renal function. **R**