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One ACE Too Many

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The Case

A 72-year-old man with coronary artery disease, diabetes, and recently diagnosed congestive heart failure presented to the emergency department (ED) with chest pain. An acute myocardial infarction was ruled out. Because his admission medication regimen did not include an angiotensin-converting enzyme (ACE) inhibitor, one was started before discharge. He had no known renal dysfunction. Two weeks later, he presented to the ED with fatigue, lethargy, and a critically elevated serum potassium level. Shortly thereafter, he suffered a cardiac arrest and died.

The patient had previously been receiving outpatient care from an ancillary clinic of the hospital. When the ED physician called to inform the clinic of the patient's death, the primary care provider recalled that the patient previously had been treated with an ACE inhibitor and had developed hyperkalemia after 1 week of therapy. The ACE inhibitor had been discontinued at that time.

The Commentary

This case illustrates how well-intentioned care can sometimes have catastrophic consequences. It also highlights how adherence to a few commonsense principles and the implementation of integrated medical records could dramatically lessen the risks of drug-related harm.

The incident described in the scenario resulted from the physician's desire to provide timely, evidence-based care. The patient had two apparent indications for an ACE inhibitor: type 2 diabetes and congestive heart failure. Unfortunately, both conditions can predispose to hyperkalemia—diabetes because of hyporeninemic hypoaldosteronism and congestive heart failure because of impaired glomerular perfusion.(1-3)

Despite the good intentions, a few noteworthy shortcomings in the process of care are evident in this case. First, the physician formulated the incorrect assumption that ACE inhibitor therapy had been previously overlooked. Phrased differently, he had insufficient information about the patient's previous medical treatment and previous response to it. Although we generally collect such information from the patient, any

clinician will attest that doing so is far from foolproof. Real-time access to the patient's past medical history would have revealed his previous intolerance of ACE inhibitors, especially if the record contained a notes field or linkage to laboratory data. Indeed, even if the record contained only a chronological listing of medication use, the ED physician could have identified previous exposure to an ACE inhibitor. Regardless of whether the patient knew the reason why the drug was discontinued, awareness of the previous exposure would have led the ED physician to be wary of reinstituting therapy.

In this patient's case, the absence of an ACE inhibitor from the medication profile is so glaring that it begs the question, "Why is it not there?" Indeed, the absence of an essential medication should generally raise a warning flag for physicians new to the patient's care. Although the initiation of an ACE inhibitor is understandable, a greater deficiency in this patient's care was the failure to communicate the treatment change to the primary care physician, who almost certainly would have stopped the drug or, at a minimum, made provisions to monitor the patient closely.

A second shortcoming was the absence of an appropriate monitoring plan. Although ACE inhibitors are generally well tolerated, like most drugs, their most worrisome adverse effects (hypotension, renal insufficiency, angioedema, and hyperkalemia) tend to occur early in therapy.(4) The front-loading of adverse events, which is characteristic of most drugs, highlights the importance of early monitoring for safety and tolerability. This is rarely the role of the emergency physician, but it is incumbent on a new prescriber to ensure that an appropriate monitoring strategy is in place.

Clinicians who read this case may ask, "How often does severe hyperkalemia complicate drug treatment with an ACE inhibitor?" The best answer is probably, "More often than clinical trials suggest." The incidence of hyperkalemia is heavily influenced by multiple factors, including the dose of the offending drug(s), use of concomitant therapies, and comorbid illnesses, particularly renal disease and diabetes mellitus.(1,2,5) Drugs that can contribute to the development of hyperkalemia are shown in the Table. A patient with left ventricular systolic dysfunction and diabetes who is receiving a maximal dose of an ACE inhibitor and 25 mg of spironolactone can have up to a 20% chance of experiencing significant hyperkalemia (K greater than 6.0 mEq/L) early in the course of treatment, depending on other risk factors.(6) How often patients actually die from hyperkalemia is a matter of speculation—because patients with severe hyperkalemia may die suddenly as outpatients, their deaths are often misattributed to heart disease rather than an adverse effect of therapy.

There are three main reasons why the incidence of hyperkalemia in the "real world" is considerably higher than that seen in randomized clinical trials (RCTs). First, RCTs typically enroll healthier patients, systematically excluding those with other risk factors for hyperkalemia (eg, advanced renal disease). Second, RCTs restrict or prohibit the concomitant use of other drugs that can cause hyperkalemia. Finally, patients enrolled in RCTs are typically monitored far more closely than those in clinical practice. All of these measures reflect the "artificiality" of the clinical trial setting, and threaten the generalizability of findings derived from RCTs.

With regard to drug-induced hyperkalemia, the disconnect between clinical trials and the real world is perhaps most striking in the example of spironolactone for the treatment of heart failure. In the Randomized Aldactone Evaluation Study (RALES), only 1.7% of heart failure patients treated with spironolactone

experienced hyperkalemia—an incidence not statistically different from that of those patients randomized to placebo (1.2%).(7) The trial's finding that spironolactone dramatically improved morbidity and mortality in patients with systolic heart failure led to an abrupt increase in spironolactone utilization but also resulted in thousands of additional hospitalizations involving hyperkalemia.(5) Moreover, there was no obvious decline in heart failure related morbidity and mortality at the population level, perhaps because of competing mortality from unrecognized hyperkalemia among outpatients.

The luxury of hindsight allows us to speculate on how the tragic outcome described in this case might have been avoided. The case appears to be one of "too many cooks in the kitchen." Although the addition of an ACE inhibitor to the patient's regimen appeared justifiable, it was not an urgent intervention, and, as such, it would have been logical to defer to a physician better able to monitor the patient's response to the drug, such as his family physician, internist, or cardiologist. The obvious downsides of this approach are the delay to treatment and the possibility that the therapy may again be overlooked. Because of these concerns, another strategy would have been to prescribe only a few days' worth of the drug and instruct the patient to contact his primary care physician soon after discharge. It is highly unlikely that this approach would have resulted in serious harm. Regardless of which strategy was selected, a quick phone call to the patient's physician would have intercepted and avoided the catastrophic outcome in this case.

Take-Home Points

- The addition of a new medication requires monitoring for adverse drug events, which typically occur early in the course of treatment.
- Medication changes should always be communicated promptly to the patient's primary care provider, who is usually best positioned to monitor for adverse events and response to treatment.
- When a medication is conspicuously absent from a patient's regimen, the physician should consider whether its absence is intentional.
- Patients enrolled in clinical trials often derive more dramatic benefits from drug treatment and experience fewer adverse events than those in real world practice.

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Table

Table. Common Drug Causes of Hyperkalemia

Drug	Notes
Aldosterone antagonists (spironolactone, eplerenone)	Dose-dependent; incidence of hyperkalemia can exceed 20% at higher doses in susceptible patients
ACE inhibitors	
Angiotensin receptor antagonists (ARBs)	
Beta-adrenergic antagonists	
Cyclosporine, tacrolimus	
Digoxin (acute overdose)	Hyperkalemia following acute overdose predicts poor outcome
Heparin	Can occur with prophylactic doses (eg, 5000 units BID)
Nonsteroidal anti-inflammatory drugs	Patients with compromised renal perfusion (eg, volume contraction, congestive heart failure) at greatest risk

Pentamidine	
Potassium supplements	
Potassium-sparing diuretics (amiloride, triamterene)	Hyperkalemia can occur even when combined with a thiazide
Salt substitutes	
Succinylcholine	
Trimethoprim	Amiloride-like effect on distal tubule; occurs at standard doses in otherwise well patients

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