Adverse Effects of Angiotensin Converting Enzyme (ACE) Inhibitors
An Update

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Contents

Summary
1. Respiratory Effects: Cough
2. Dermatological Effects
   2.1 Rash
   2.2 Pemphigoid Reaction
   2.3 Angioedema
   2.4 Alopecia
   2.5 Flushing
3. Haematological Effects
   3.1 Anaemia
   3.2 Neutropenia
   3.3 Thrombocytopenia
4. Central Nervous System Effects
   4.1 General Effects
   4.2 Deterioration in Huntington's Disease
   4.3 Depression
5. Endocrine/Metabolic Effects
   5.1 Sodium and Potassium Balance
   5.2 Metabolic Effects
   5.3 Serum Chemistry
   5.4 Gynaecomastia
6. Gastrointestinal Effects
   6.1 Dyspepsia
   6.2 Taste Disturbances
   6.3 Liver
7. Cardiovascular Effects
   7.1 Hypotension
8. Renal Effects
   8.1 Functional Renal Insufficiency
      8.1.1 High-Risk Groups
9. Other Effects
10. Use in Pregnancy
11. Use in Children
Summary

The angiotensin converting enzyme (ACE) inhibitors are a group of effective drugs with a unique mechanism of action. These drugs have proven to be useful for hypertension and congestive heart failure. Early clinical trials of captopril used doses that are now known to be inappropriately high, and dose-related adverse effects were observed frequently. The recognition that lower doses are effective has reduced the incidence of adverse reactions and resulted in improved patient tolerance. When patients are properly selected and correctable risk factors are removed, serious side effects are uncommon. Unfortunately, the early reputation of nephrotoxicity persists, as does the belief that significant blood dyscrasias, endocrine effects and rash are serious risks for the average patient.

After wide use of captopril, enalapril and lisinopril, and investigational trials of nearly a dozen newer agents, a sufficiency of clinical observation, experimental evidence and accurate postmarketing recording of events is accumulating to allow insight into the major toxicities with regard to more intelligent patient selection, more rational dosing and proper identification of risk factors.

The most common adverse reactions are cough and skin rash. It appears that the agents are generally not cross-reactive with regard to skin rash, although it is not clear whether this effect is drug-specific or class-specific with regard to cough.

Statistically but not clinically significant lowering of haemoglobin and hematocrit is common; these effects are inconsequential in most patients. Neutropenia, once thought to be prevalent, now appears to be so only in patients with autoimmune or collagen-vascular disease; the majority of patients outside these groups are at low risk.

Hyperkalaemia is a frequent occurrence. This should not be surprising in view of the effect of the ACE inhibitors on plasma aldosterone. When dietary potassium intake is regulated and sources of altered potassium excretion are identified, hyperkalaemia is seldom a serious problem. Identification of sodium and water deficits allows correction before the drugs are started, and the frequency of hypotension and hyperkalaemia caused by the drugs is quite low if these factors are properly managed.

An unexpected finding emerging in recent years is the dry cough associated with ACE inhibitor therapy. Its mechanism is not definitely known. Nonsteroidal anti-inflammatory drugs may control this symptom in some patients.

The frequent observation of proteinuria in patients taking ACE inhibitors has gained notice and sometimes caused undue alarm. It is difficult to separate disease effects in diabetes and hypertension from true drug effects. Proteinuria may be only slightly more common with drug therapy than in the population of patients with these diseases who are not taking ACE inhibitors. The drugs now appear to be directly nephrotoxic only in rare cases. In many patient populations, they may even slow the advance of renal disease or be protective of renal function. Risk factors for the development of functional renal insufficiency have been identified and high risk patients can either avoid ACE inhibitor therapy or start at lower doses.

The drugs still cannot be recommended for use in pregnancy except in circumstances where they are the only means of managing life-threatening hypertension. ACE inhibitors appear to be safe and effective for severe childhood hypertension, but not in neonates.

The majority of clinical experience, especially postmarketing studies, has dealt with captopril and enalapril. Experience continues to accumulate with lisinopril, ramipril, benazepril and other new agents, but to date these appear to be indistinguishable from enalapril in their side effect profiles.

The ACE inhibitors appear to be attractive choices for managing hypertension of all degrees, and congestive heart failure in all stages. With intelligent use, they offer a reasonably safe alternative to older therapies and may have significant advantages in well selected patients.