Louisiana Drug Utilization Review (LADUR) Education

Identifying the Risks Associated with Nonsteroidal Anti-Inflammatory Drugs And Heart Failure

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Issues

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• Much controversy exists associating nonsteroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX-2) inhibitors in exacerbating new-onset heart failure and/or relapses of heart failure.

Introduction

The prevalence of heart failure is increasing as the population ages in the United States. Now, approximately five million people in the U.S. have heart failure with an expected 550,000 new cases annually. The incidence of heart failure doubles with every decade reaching 10% by age 75. Five-year mortality rates remain high at 50% regardless of medical advances.

Heart failure is a progressive disorder of the myocardium that leads to the inability of the heart to meet the metabolic demands of tissues in the body. Systolic (contraction) dysfunction is the most common abnormality followed by diastolic (relaxation) dysfunction. Frequently, systolic and diastolic dysfunctions co-exist in heart failure patients. Coronary heart disease is the most common condition leading to heart failure.

In the setting of heart failure, the body depends upon compensatory mechanisms for maintaining adequate cardiac output such as neurohormonal (norepinephrine) and neuroendocrine (renin-angiotensin-aldosterone system) changes, vasoconstriction, an increase in pre-load that will lead to an increase in cardiac output, and ventricular hypertrophy and remodeling of the myocardium. Sudden death in heart failure occurs in about 40% of patients, possibly caused by serious ventricular arrythmias, contributing substantially to the cause of death for this patient population. Of note, prostaglandins play a significant role in maintaining peripheral blood flow and renal function in chronic heart failure.

Much controversy exists associating nonsteroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX-2) inhibitors in exacerbating new-onset heart failure and/or relapses of heart failure. NSAIDs have been implicated in increasing the risk of heart failure hospitalization by two-fold in patients with underlying cardiovascular disease. The beneficial and harmful effects of NSAIDs are directly related to their inhibition of prostaglandin synthesis, as many elderly patients may be dependent upon prostaglandins for maintenance of their renal function previous to NSAID usage, leading to a decrease in renal function and

possibly causing heart failure to precipitate. Inhibition of prostaglandins can also lead to an increased systemic vascular resistance. Hypertension and renal insufficiency have been well recognized as precipitous causes of heart failure.

Adverse drug reactions (ADRs) account for significant morbidity and mortality in patients every year. Reportedly, on an annual basis there are about 2 million ADRs with as many as 100,000 deaths nationally, making ADRs the fourth leading cause of death and costing 136 billion dollars. Many epidemiological studies have been conducted identifying several risk factors of heart failure development with NSAID usage (Table 1).

Table 1: Identified Risk Factors for Heart Failure with NSAID Usage:

Risk Factor:
Age > 65 years
Cardiovascular disease
Respiratory disease
First 30 days of NSAID therapy
>2 grams of Acetaminophen daily
Hypertension due to an underlying renal cause
Obesity
Current or past smoking history

Studies

Rodriguez, et al., (Epidemiology 2003; 14:240-46) conducted a nested, case-control, observational study of newly diagnosed heart failure patients in the United Kingdom. They studied 857 confirmed cases of new-onset heart failure and 5000 controls. The authors concluded that risk factors for developing heart failure included obesity (BMI>30), current or past smoking history, and heart and respiratory disease. Alcohol intake was not a factor; furthermore, renal failure was not significant (CI 0.91-3.54). However, there were few patients (n=46) in this group.

The most common indication for NSAID usage in the study group was osteoarthritis, 52% were male, and 70% were more than 69 years of age. NSAID usage was associated with a 60% increased risk of heart failure, with the greatest risk in the first 30 days of NSAID therapy (RR = 2.1; 1.4-3.3). Risks based on chemical class of NSAIDs can be found in Table 2. The longer the duration (>30 days) of NSAID therapy resulted in a decreased risk of heart failure and fell quickly upon NSAID discontinuation. Half-life and level of dosage were insignificant as risk factors for causing heart failure.

Table 2: Relative Risks of Heart Failure Based on NSAID Chemical Class:

Chemical Class:	RR	95% Confidence Interval
Propionic Acid derivatives	1.7	1.2-2.4
Hetoaryl acetic acids	1.1	0.7-1.8
Indole and Indene acetic Acids	2.4	1.1-5.3
Other Classes	2.6	1.2-5.4

Regarding the users of antihypertensive medications and NSAIDs, the RR was 1.6 (CI 1.2-2.3) versus only 1.3 (CI: 0.8-2.1) for patients using NSAIDs but not currently on any antihypertensives. Furthermore, when the cause of the heart failure was hypertension, the risk associated with NSAIDs was increased, and even more so when the hypertension is related to a renal versus a non-renal cause. Regarding antihypertensive medications, angiotensin converting enzyme (ACE) inhibitors used concurrently with NSAIDs had the greatest risk of developing heart failure compared to other antihypertensive medications.

Acetaminophen, in doses greater than two grams/day as compared to lower doses (RR 1.77; 1.35-2.31), was observed as a significant risk factor for heart failure in the first month of use (RR 1.33; 1.06-1.67) when compared to non-users. This may be explained by the fact that in-vitro analysis of acetaminophen doses greater than two grams has exhibited substantial inhibition of cyclooxygenase. The risk of heart failure with acetaminophen was found when the drug was used as a single entity or when used in combination products. However, aspirin has not been shown to have an increased incidence of heart failure.

Cyclooxygenase-2 (COX-2) inhibitors became immensely popular upon their introduction into the marketplace, rapidly replacing their non-selective counterparts due to the expectation of lower gastrointestinal side effects. Studies comparing selective COX-2 inhibitors and their effect on heart failure have been conducted.

In two retrospective cohort trials, celecoxib was found to be safer than rofecoxib and non-selective NSAIDs for heart failure admissions.

Furthermore, the authors speculate that there is not a class effect with COX-2 inhibitors. It should be noted that these trials were criticized for not adequately accounting for confounders.

Conclusion

Elderly patients may have many reasons to require NSAID therapy, such as osteoarthritis, but are also at an increased risk for heart failure as they age. Non-specific NSAIDs, regardless of chemical class, can lead to new-onset heart

failure, especially in the first thirty days of therapy in elderly patients. Caution is warranted in patients with diabetes, hypertension, renal disease, cardiovascular disease and pulmonary disease when starting NSAID therapy. Other risk factors to be taken into consideration are age greater than 65 years, past or current smoking history, and obesity. Aspirin usage is not a factor in new onset heart failure. COX-2 inhibitors have also been studied, and rofecoxib, which has been withdrawn from the market, appears to have a higher incidence of heart failure than celecoxib, possibly indicating that the risk is not a class effect.

References Available Upon Request