Incluida en ISI-WOK, MEDLINE, EMBASE, IME, IBECS, SCIELO
nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Original article

Acute kidney injury secondary to a combination of renin-angiotensin system inhibitors, diuretics and NSAIDS: "The Triple Whammy"

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ARTICLE INFO

Sent for Review: 24 Oct. 2014
Accepted on: 16 Dec. 2014

Key Words:
Acute kidney injury
Antihypertensive agents
Diuretics
Drug interactions
Anti-inflammatory agents

ABSTRACT

Background: Renin-angiotensin system inhibitors (ACEI/ARB-II), diuretics and NSAIDs, a combination known as "Triple Whammy", can result in decreased glomerular filtration rate (GFR) and acute kidney injury (AKI).
Objectives: To describe the incidence of AKI for each drug type and their combinations. To define the profile of patients admitted for drug-related AKI secondary to Triple Whammy drugs (AKITW), with an assessment of costs and mortality.
Methods: A retrospective observational 15-month study developed in three stages:
- First: a cross-sectional stage to identify and describe hospitalizations due to AKITW.
- Second: a follow-up stage of an outpatient cohort consuming these drugs (15,307 subjects).
- Third: a cohort stage to assess costs and mortality, which compared 62 hospitalized patients with AKITW and 62 without AKI, paired by medical specialty, sex, age and comorbidity according to their Clinical Risk Groups.

Results: There were 85 hospitalization episodes due to AKITW, and 78% of patients were over the age of 70. The incidence of AKITW in the population was 3.40 cases/1000 users/year (95% CI: 2.59–4.45). By categories, these were: NSAIDs + diuretics 8.99 (95% CI: 3.16–25.3); Triple Whammy 8.82 (95% CI: 4.4–17.3); ACEI/ARB-II + diuretics 6.87 (95% CI: 4.81–9.82); and monotherapy with diuretics 3.31 (95% CI: 1.39–7.85). Mean hospital stay was 7.6 days (SD 6.4), and mean avoidable costs were estimated at €214,604/100,000 inhabitants/year. Mortality

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http://dx.doi.org/10.3265/Nefrologia.pre2014.Dec.12800

during hospitalization and at 12 months was 11.3% and 38.7% respectively, and there were no significant differences when compared with the control group.
Conclusions: Treatment with ACEI, ARB-II, diuretics and/or NSAIDs shows a high incidence of hospitalization episodes due to AKI; diuretics as monotherapy or dual and triple combination therapy cause the highest incidence. AKITW involves high health care costs and avoidable mortality.

Fracaso renal agudo secundario a combinación de inhibidores del sistema renina-angiotensina, diuréticos y AINES. "La Triple Whammy"

Palabras clave:
Lesión renal aguda
Agentes antiinflamatorios
Agentes antihipertensivos
Diuréticos
Interacciones farmacológicas

RESUMEN

Introducción: Inhibidores del sistema renina-angiotensina (IECAS/ARA II), diuréticos y AINES, combinación conocida como "Triple Whammy", pueden producir descenso de filtrado glomerular y fracaso renal agudo (FRA).
Objetivos: Describir la incidencia de FRA para cada tipo de fármaco y sus combinaciones. Caracterizar el perfil de paciente que ingresa por FRA extrahospitalario secundario a fármacos de la Triple Whammy (FRAETW), evaluando costes y mortalidad.
Métodos: estudio observacional retrospectivo realizado durante 15 meses y desarrollado en tres etapas:
- 1º Etapa transversal de identificación y descripción de los ingresos hospitalarios por FRAETW.
- 2º Etapa de seguimiento de una cohorte ambulatoria consumidora de estos fármacos (15.307 consumidores)
- 3º Etapa de cohortes para evaluar costes y mortalidad, contrastando 62 pacientes ingresados con FRAETW, con 62 pacientes sin FRA, apareados por especialidad médica, sexo, edad y comorbilidad según Clinical Risk Groups.

Resultados: 85 ingresos por FRAETW, 78% mayores de 70 años. Incidencia poblacional de FRAETW: 3,40 casos/1.000 consumidores/año (IC95% 2,59-4,45). Por categorías: AINES + diuréticos 8,99(IC95% 3,16-25,3), la "Triple Whammy" 8,82(IC 95% 4,4-17,3), IECA/ARA II + diuréticos 6,87(IC95% 4,81-9,82) y la monoterapia con diuréticos 3,31(IC95% 1,39-7,85). Estancia media 7,6 días (DE 6,4), estimándose coste medio evitable de 214.604 €/100.000 habitantes/año. Mortalidad del 11,3% durante el ingreso y del 38,7% a los 12 meses, sin diferencias significativas con los controles.
Conclusiones: El tratamiento con IECA, ARA II, diuréticos y/o AINES presenta elevada incidencia de ingreso por FRA, siendo los diuréticos en monoterapia, doble y triple terapia combinada los que ocasionan la mayor incidencia. El FRAETW supone elevados costes sanitarios y muertes evitables.

Introduction

The combination of renin-angiotensin system inhibitor (ACEI or ARB-II) antihypertensive drugs with diuretics, which is often associated with analgesic treatments including non-steroidal anti-inflammatory drugs (NSAIDs) in senior patients, may cause acute kidney injury (AKI). These drug interactions have not been well studied in the literature.[1-4]

In 1996, the incidence of AKI in Spain was 209 cases/million adults/year[5] according to a study by Liaño, et al., conducted in the Madrid Community. The 2002 study by L.M. Lou, et al.[6], which was conducted at a Spanish district hospital with characteristics similar to ours, indicated that 79% of hospitalizations due to AKI originated outside the hospital. The cause was volume depletion in 34.2% of cases, a datum that highlighted the elevated incidence of antihypertensive treatments (primarily renin-angiotensin system inhibitors) and/or diuretics as coadjuvant factors for AKI.

However, the study of drug-related acute kidney injury has received little attention in the literature; meanwhile, its implications in terms of increased mortality, days of hospitaliza-