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Original Article

Efficiency of Naproxen/Esomeprazole in Association for Osteoarthrosis Treatment in Spain☆

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ABSTRACT

Objective: To assess, from the perspective of the National Healthcare System, the efficiency of a fixed-dose combination of naproxen and esomeprazole (naproxen/esomeprazole) in the treatment of osteoarthritis (OA) compared to other NSAID, alone or in combination with a proton pump inhibitor (PPI).
Methods: A Markov model was used; it included different health states defined by gastrointestinal (GI) events: dyspepsia, symptomatic or complicated ulcer; or cardiovascular (CV) events: myocardial infarction, stroke or heart failure. The model is similar to the one used by NICE in its NSAID evaluation of OA published in 2008.

The total costs (€, 2012), including drug and event-related costs, and the health outcomes expressed in quality-adjusted life years (QALY) were estimated in patients with increased GI risk, aged 65 or over, for a 1-year time horizon and a 6-month treatment with celecoxib (200 mg/day), celecoxib+PPI, diclofenac (150 mg/day)+PPI, etoricoxib (60 mg/day), etoricoxib+PPI, ibuprofen (1800 mg/day)+PPI, naproxen (1000 mg/day)+PPI or naproxen/esomeprazole (naproxen 1000 mg/esomeprazole 40 mg/day). The selected PPI was omeprazole (20 mg/day).
Results: Naproxen/esomeprazole was a dominant strategy (more effective and less costly) compared to celecoxib, etoricoxib and diclofenac+PPI. Celecoxib+PPI and etoricoxib+PPI were more effective.

Considering a cost-effectiveness threshold of € 30 000 per additional QALY, naproxen/esomeprazole was cost-effective compared to ibuprofen+PPI and naproxen+PPI with incremental cost-effectiveness ratios (ICER) of € 15 154 and € 5202 per additional QALY, respectively.
Conclusions: A fixed-dose combination of naproxen and esomeprazole is a cost-effective, and even dominant, alternative compared to other options in OA patients with increased GI risk.

Eficiencia de la combinación naproxeno/esomeprazol para el tratamiento de la artrosis en España

Palabras clave:
Artrosis
Antiinflamatorios no esteroideos
Coste-utilidad

RESUMEN

Objetivo: Evaluar, desde la perspectiva del Sistema Nacional de Salud, la eficiencia de la combinación a dosis fija de naproxeno y esomeprazol (naproxeno/esomeprazol) en artrosis frente a otros AINE en monoterapia o combinados con un inhibidor de la bomba de protones (IBP).
Métodos: Se empleó un modelo de Markov con estados de salud definidos por episodios gastrointestinales (GI): dispepsia, úlcera péptica sintomática o complicada; o cardiovasculares (CV): infarto agudo de miocardio, ictus o insuficiencia cardiaca. El modelo es semejante al utilizado por el NICE en su evaluación de AINE en artrosis publicada en 2008.

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Se estimaron, en un horizonte temporal de 1 año (ciclos de 3 meses), los costes totales (€, 2012), incluyendo coste farmacológico y de manejo de episodios, y los resultados en salud, expresados en años de vida ajustados por calidad (AVAC), en pacientes mayores de 65 años con riesgo GI aumentado, tras 6 meses de tratamiento con celecoxib (200 mg/día), celecoxib + IBP, diclofenaco (150 mg/día) + IBP, etoricoxib (60 mg/día), etoricoxib + IBP, ibuprofeno (1.800 mg/día) + IBP, naproxeno (1.000 mg/día) + IBP o naproxeno/esomeprazol (naproxeno 1.000 mg/esomeprazol 40 mg/día). El IBP fue omeprazol (20 mg/día).
Resultados: Naproxeno/esomeprazol resultó dominante (más efectivo y menor coste) respecto a celecoxib, etoricoxib y diclofenaco + IBP. Celecoxib + IBP y etoricoxib + IBP fueron más efectivos.

Considerando un umbral de 30.000 €/AVAC adicional, naproxeno/esomeprazol resultó coste-efectivo respecto a ibuprofeno + IBP y naproxeno + IBP con valores de relación coste-efectividad incremental de 15.154 € y 5.202 €/AVAC adicional, respectivamente.
Conclusiones: La combinación a dosis fijas de naproxeno y esomeprazol en pacientes con artrosis y riesgo GI aumentado es una alternativa coste-efectiva e incluso dominante frente a otras opciones.

Introduction

Osteoarthritis is the most common joint disease and a major cause of functional disability and impaired quality of life.[1] It is one of the most common reasons for visits to primary care and has a high socioeconomic impact[2] with an estimated annual cost of € 1502 per patient, resulting in a total expense of 511 billion euros a year in Spain.[3] It occurs in all populations and its incidence increases with age. It is estimated to affect 85% of the elderly population and disables 10% of people over 60 years, mainly women.[2] The prevalence of knee and hands osteoarthritis in the Spanish population was estimated at 10.2% and 6.2%, respectively.[1]

The goals of osteoarthritis treatment are to relieve pain, improve joint function and delay disease progression in terms of structural joint damage, preventing the toxic effects of treatment. In choosing the therapeutic strategy, clinicians can turn to the recommendations of the *European League Against Rheumatism* (EULAR),[4] and the *American College of Rheumatology* (ACR),[5] as well as the consensus documents of the Spanish Society of Rheumatology (SER)[6] or to the guidelines of the *Osteoarthritis Research Society International* (OARSI).[7]

Most of the therapeutic goals can be achieved by treatment with various non-selective nonsteroidal anti-inflammatory drugs (NSAIDs). However, NSAID use is frequently associated with gastrointestinal disorders (GI) which can range from mild discomfort to severe adverse events such as perforations and bleeding; this is associated with a high consumption of health resources.[8] Concomitant administration of proton pump inhibitors (PPIs) has shown an inverse relationship with the development of GI episodes, strongly influenced by the adherence to PPIs.[9]

The introduction of selective cyclooxygenase inhibitors 2 (ICOX-2) of similar efficacy provided an interesting alternative for improving the toxicity profile in terms of GI events compared to traditional NSAIDs. However, their widespread use has been associated to an increase of cardiovascular events (CV), some of which also involve traditional NSAIDs, with the possible exception of naproxen, which has not been associated with increased cardiovascular events.[10]

Therefore, strategies can be employed with NSAID use, both traditional and ICOX-2 of similar efficacy but different safety profiles, which affect the quality of life related to the health of patients with osteoarthritis.

The fact that health care resources are limited requires that prescription be an act that considers the most effective among the available drugs and selects the most effective in treating the disease in question, prescribing that which enables a lower incremental cost per additional unit of effectiveness.

The fixed dose combination of naproxen and esomeprazole[a] (naproxen/esomeprazole) combines the efficiency of naproxen as an NSAID, with a lower incidence of NSAID-associated ulcers and better tolerated in the upper digestive tract, due to its association to esomeprazole, a PPI.[11] Its efficacy in osteoarthritis is equivalent to ICOX-2 and has proven to maintain its profile of GI and CV safety, even in the long term.[12]

The objective of this analysis was to conduct an assessment of the efficiency of naproxen/esomeprazole as an alternative therapy in patients with osteoarthritis compared to other NSAIDs available in Spain, both traditional and ICOX-2, alone or administered with a PPI.

Materials and Methods

Model Structure

We used a Markov model, developed in Microsoft Excel 2007, to simulate the course of the disease in a hypothetical cohort of patients passing through different states of health. These models are commonly used in simulations of chronic diseases. The health states should be mutually exclusive, so the patient at all times can only be in one of these states, remaining for a uniform period of time, called a cycle. At the end of each cycle the patient may pass or *move* to another state according to transition probabilities.

In this case eight health states were created among which patients could move in defined cycles of 3 months. From the initial "without incident" state, the patient evolves to the "death" state or 6 other states derived from the appearance of a clinical event: GI-dyspepsia, symptomatic or complicated ulcer or ulcer-CV-myocardial infarction (MI), stroke, or congestive heart failure (CHF) (Fig. 1).

Except for dyspepsia, the remaining episodes were considered serious. After a severe episode, the patient remained in the corresponding post-episode state for the rest of the simulation or until transition to the absorbing health state (death). However, to consider the fact that, in clinical practice, a patient may experience later episodes, and that the probability of occurrence of these events is highest in patients who have had a previous episode, the cost and the associated usefulness of each severe postepisode state were weighted to take into account other possible future episodes. Patients with dyspepsia could remain in this state for the rest of the simulation, resulting in a serious episode with the implications described, or die.

[a] This fixed dose combination is marketed in Spain as modified-release tablets containing naproxen with enteric coating and film-coated esomeprazole (as magnesium trihydrate).