United Kingdom experience with alendronate and oesophageal reactions

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SUMMARY

Alendronate is indicated for the treatment of osteoporosis in post-menopausal women. Although the drug has been associated with reports of severe oesophagitis, there have been no studies establishing the incidence of such reactions. Information was collected on 1523 patients included in a study conducted by means of prescription–event monitoring. Dyspepsia, nausea/vomiting, and abdominal pain were the most frequently reported events in the first month of treatment. After follow-up, 20 patients (1.3%) experienced oesophageal events that were considered to be possibly related to alendronate.

Keywords: oesophageal disease, osteoporosis, prescription event monitoring.

Introduction

WITH an increasingly elderly proportion of the population, osteoporosis is set to remain a significant public health concern. Alendronate is an amino-biphosphonate used to treat osteoporosis in post-menopausal women. Although alendronate has been associated with reports of severe oesophagitis,[1] there have been no studies establishing the incidence of such reactions.

Method

Patients were identified from prescription data supplied electronically and in confidence by the Prescription Pricing Authority immediately after the United Kingdom (UK) launch of alendronate. Questionnaires ('green forms') were posted to prescribers in April/May 1996, three to six months after the first prescription for each patient. One questionnaire was sent for each patient, and no doctor was sent more than four questionnaires per month. Questionnaires asked about age, indication, starting and stopping dates, events during and after treatment, and reasons for discontinuation.

The term 'event' includes 'any new diagnosis, reason for referral, admission to hospital, unexpected deterioration (or improvement) in a concurrent illness, suspected drug reaction, or any other complaint considered of sufficient importance to enter in the patient's notes'.

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Events were converted to DSRU (Drug Safety Research Unit) dictionary terms. A daily quality assessment procedure examined the accuracy of data entry.

Incidence densities (IDs) were calculated for events reported during treatment. IDs provided a measure of relative frequency and allowed contextual comparison between events.

$$ID_t = \frac{\text{Number of reports of an event during treatment for period } t}{\text{Number of patient–months of treatment for period } t} \times 1000$$

Reports of dysphagia, gastrointestinal haemorrhage, haematemesis, melaena, oesophageal reflux, oesophageal stricture, oesophageal ulcer, and oesophagitis were examined. These and additional serious events were followed up by contacting the patient's general practitioner (GP). The causal relationship between alendronate and individual events was assessed using the following categories: probable, possible, unlikely, or not assessable. Assessment took account of whether the event was the reason for discontinuation, resolution of symptoms after discontinuation, recurrence of symptoms upon re-exposure, concurrent medication, concurrent disorders, and past history.

Results

A total of 1605 (63.3%) out of 2536 questionnaires posted were returned. Of these, 82 were classified as void. The final cohort was 1523 (137 men, mean age 63.3 ± 13.4 years, 1378 women, mean age 69.3 ± 10.7 years, and eight whose sex was unspecified).

Dyspepsia, nausea/vomiting, and abdominal pain were the most frequent reasons for discontinuing alendronate and the most frequently reported events (Table 1).

After follow-up, two reports of oesophageal stricture, seven reports of oesophagitis, five reports of oesophageal reflux, and six reports of dysphagia were considered to be possibly related to alendronate. A total of 20 (1.3%) patients therefore experienced possible oesophageal reactions.

Discussion

The technique, strengths and weaknesses of prescription–event monitoring (PEM) have been described elsewhere.[2] This cohort represents the first batch of patients prescribed alendronate in England and includes those who would normally be treated in 'everyday' practice. GPs were asked to report all 'events' recorded in patients' notes. By removing the need to give an opinion about causality, this provided the possibility of identifying reactions that doctors had not suspected as being caused by medication. We cannot estimate the degree of compliance with dispensed alendronate. Information on co-medication was generally incomplete but was obtained from individual follow-up enquiries. There were no data on 'over-the-counter' medication.

We have no method of comparing the population of patients whose doctors returned questionnaires with those whose doctors did not. A response of 63.3% is satisfactory for general practice surveys in general[3] and substantial compared with spontaneous reporting schemes.[4]

The broad term 'dyspepsia' (Table 1) included reports of 'dyspepsia', 'heartburn', 'oesophagitis', and 'oesophageal reflux'. The incidence of 'dyspepsia' alone in month 1 (ID_1) was 13.0 per

Table 1. Ranked incidence densities during the first month of treatment (ID_1) and during the whole treatment period (ID_A) per 1000 patient–months of treatment.

Denominators (patient–months of treatment)	For ID_1		For ID_A	
Male	125		658	
Female	1256		7392	
Sex not specified	7		36	
Total	1388		8085	
Event	Number of reports in month 1	ID_1	Number of reports in total treatment period	ID_A
Nausea, vomiting	34	24.5	67	8.3
Dyspepsia	27	19.5	91	11.3
Pain abdomen	27	19.5	61	7.5
Respiratory tract infection	23	16.6	117	14.5
Malaise, lassitude	15	10.8	43	5.3
Diarrhoea	13	9.4	39	4.8
Pain back	10	7.2	43	5.3
Asthma, wheezing	8	5.8	19	2.4
Non-compliance	8	5.8	24	3.0
Urinary tract infection	8	5.8	31	3.8
Constipation	7	5.0	17	2.1
Cough	7	5.0	22	2.7
Dizziness	7	5.0	15	1.9
Pain joint	7	5.0	33	4.1
Headache, migraine	6	4.3	20	2.5

1000 patient–months. This compares crudely with an ID_1 of 4.5 per 1000 patient–months for women aged over 60 years who were prescribed 10 other drugs recently studied by PEM (lamotrigine, vigabatrin, bambuterol, moclobemide, perindopril, risperidone, gabapentin, fluvastatin, losartan, and venlafaxine).

A large review of post-marketing surveillance data for alendronate has been published.[1] A total of 1213 reports of adverse events were received for an estimated 475 000 patients worldwide (spontaneous reporting to the manufacturer). Of these, 199 (0.04%) were oesophageal events. This compares with 1.3% assessed after follow-up in our study. Factors thought to contribute to the development of oesophagitis include taking alendronate with less than 180 ml of water or in a supine position, lying down after ingestion, continuing treatment despite oesophageal symptoms, and pre-existing oesophageal disorders prolonging mucosal exposure.[1] The summary of product characteristics was revised in April 1996 to include warnings about oesophageal reactions. At the same time, UK doctors received additional information concerning alendronate and oesophageal problems.[5,6] This coincided with the timing of our questionnaires. However, GPs were asked to report events already recorded in the patient's notes. We examined event dates for oesophageal reports. Publicity bias did not account for the number of reports of dyspepsia and individual oesophageal reactions.

Incidence figures for events are displayed. These are valuable when discussing the likelihood of individual patients developing possible side effects.

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