

Learning points

Well known adverse drug reactions can sometimes be difficult to pinpoint

Certain adverse drug reactions are fairly commonplace, and we are all very familiar with them. However, it is sometimes just this familiarity that makes them difficult to track down, as Annett Blochberger explains

Iatrogenic disease is an established cause of hospital admissions in the elderly — accounting for 5–17% of hospital admissions and increased morbidity during inpatient stay.¹ Many of the adverse drug reactions may be prevented beforehand. In addition to giving consideration to whether the patient's body is capable of handling the medication, the patient's mental capacity and ability must be taken into account. To assess the appropriateness of the prescribed medication, the *National Service Framework (NSF) for older people* recommends regular reviews for patients aged more than 75 years.¹

This case describes a recognised, but misinterpreted, adverse drug reaction (ADR) experienced by an elderly resident in a care home. The following learning outcomes are anticipated:

- awareness for medication review if patient's ability of handling medication changes
- assessment of adverse drug reactions
- importance of adherence to instructions for administration
- principles for prescribing in the elderly
- evidence for primary and secondary prevention of osteoporosis in men.

The case

Background

Mr B is an 87 year-old man who has lived in a care home since September 2006. His level of care is very high because he suffers

from dementia. The past medical history was fairly unremarkable until August 2005 when he presented with frequent falls. The cause of the falls was investigated and assessed as being mechanical. Mr B is prone to seizures secondary to infections.

Past medical history

The past medical history is as follows:

1991	Osteoarthritis left hip
1995	Hiatus hernia
1995	Irritable bowel syndrome
1997	Osteoarthritis shoulder
2005	Vitamin B12 deficiency
2005	Falls
2006	Transient ischemic attack. He was found to have a normal CT.

Sequence of events

The chronology of Mr B's recent problems, which began in November 2006, is listed below.

November 2006

Mr B experienced a mechanical fall, which led to subsequent admission to hospital. He

returned to the home with the recommendation to his GP that a bisphosphonate should be prescribed because in falling he had fractured his clavicle. He was prescribed ibandronic acid 150mg once monthly by the GP.

February 2007

A medication review, during a multi-disciplinary meeting, led to the successful withdrawal of codeine and lorazepam, which are associated with sedation and falls. A blood test showed no abnormalities in terms of full blood count (FBC) or vitamin B12 levels so the planned hydroxocobalamin was withheld.

March 2007

Mr B was readmitted to hospital after experiencing two episodes of grand mal seizures secondary to aspiration pneumonia/sepsis. During admission he experienced another seizure and phenytoin was started. A CT of the head was performed, which showed no bleeding. However, there was evidence of small vessel disease, which is consistent with Mr B's diagnosis of dementia. The infection improved with antibiotics, Mr B experienced no further seizures and was subsequently discharged home taking phenytoin suspension 270mg once daily.

April 2007

The patient appeared drowsy. Despite the absence of other signs of toxicity, the GP requested a phenytoin level. The total plasma phenytoin level was subtherapeutic

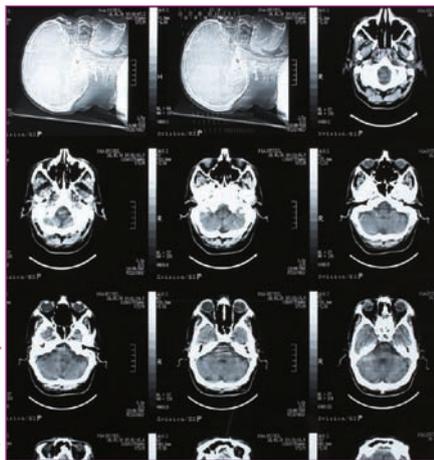


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Learning points

Mr B was examined by his GP who noted an ulcer on the tongue at the middle of the mouth, and his lips were red with cuts. Symptoms started to develop about four days after administration of the monthly ibandronic acid tablet.

at 6.3 mg/L (normal range 10–20 mg/L). Because Mr B had a low serum albumin level of 31g/L (reference range 40–60g/L) to which phenytoin is highly bound it was felt that his plasma phenytoin level would not give a true reflection of the therapeutically active plasma unbound level, which would have been higher than anticipated. Therefore, an estimation of the unbound fraction was made from the serum albumin level and this was used to predict the corresponding plasma phenytoin level that would have been found if Mr B had normal levels of albumin and therefore of protein binding. This was estimated at 7.9g/L. The decision was made not to change the dose because Mr B was not experiencing any seizures.



May/June 2007

Another two grand mal seizures of increasing duration occurred and Mr B was referred back to hospital. During admission he experienced another seizure with a prolonged post-ictal period. He recovered after 72 hours. During the hospital stay a low platelet count was noticed. Due to lack of phenytoin efficacy and thrombocytopenia he was started on levetiracetam. Because levetiracetam is known to cause drowsiness and thrombocytopenia, careful titration of the dose and monitoring of

FBC was advised. Mr B was also given a course of amoxicillin and erythromycin because of suspected pneumonia. The infection improved, no further seizures occurred and he was discharged home.

Five days after discharge he developed sore gums. He was seen by a nurse practitioner, who recommended Bonjela. The cause of the sore gums was thought to be Fixodent®, a denture adhesive product used to keep dentures in place. He had previously used a different adhesive product without any problems.

One day later, the whole mouth was very sore and Mr B experienced difficulties swallowing. The inflammation appeared to have spread over the mucosa of the inner cheeks, the upper palate and the pharynx. The prescription was changed to Nystatin, based on the diagnosis of oral thrush. The current course of antibiotics was considered to be the cause.

One day later, the condition deteriorated, blisters had spread over the whole mucosa of the mouth, including the upper palate and the pharynx. He also started to develop blisters on the lips. The nurse practitioner referred the patient to a GP because she felt the clinical picture differed greatly from oral thrush. The GP agreed and thought the picture resembled more a chemical injury. It was decided to leave the treatment as it was and get Mr B reviewed by his usual GP.

Mr B was then examined by his GP who noted an ulcer on the tongue at the middle of the mouth, and his lips were red with cuts. The nurses reported bleeding from mouth and lips. His overall condition was improving, he was able to swallow a soft diet. The course of Nystatin was continued. In the meantime Mr B was seen by a dentist, who added Triad Cortyl to the prescription.

At this point the nurse practitioner mentioned Mr B's unusual condition to the care home's pharmacist who explained that ibandronic acid, if not administered properly could cause severe ulcers. However, the answer from a staff nurse reassured the pharmacist that ibandronic acid was being given correctly so different potential causes for the ulceration were explored.

The case was discussed at length with the nurse practitioner and the following options considered:

1. **Levetiracetam.** A recently started drug, but there was no mention any side-effects resembling those found in this case in the SPC or from the manufacturer.
2. **Vitamin B12 deficiency.** Although a sore, red tongue can be associated with vitamin B12 deficiency Mr B's B12 levels were normal and he was no longer being treated with B12 injections.
3. **Fixodent®.** This was used the first time a couple of days before the ulcers appeared but considered as a fairly unlikely cause because of the extent of the injuries to the lips and pharynx.

Over subsequent days the nurse practitioner reported that Mr B's condition was improving. She also reported that Mr B was sometimes holding his food in his mouth for a long time. This fact triggered another enquiry with the nursing staff, who again denied any previous swallowing difficulties. However, the pharmacist established that symptoms started to develop about four days after administration of the monthly ibandronic acid tablet. As no other cause seemed plausible, the pharmacist had another conversation with the staff nurse who admitted Mr B's swallowing may not be so good after all. It was established that Mr B is very slow with taking his medication and food. This may be attributable to his drowsiness and tiredness as well as the decline in his mental condition.

The pharmacist subsequently informed the GP that the cause of the injuries was established. Ibandronic acid was discontinued and the resident is recovering slowly from the injuries.

Analysis of the delay in finding the cause

The condition was improving so one may argue that the nurses did not see the need to investigate the cause of the injuries. Also, the main carers were convinced that Fixodent® was the reason for Mr B's sore mouth and it was not administered again.

Other 'red herrings' were the introduction of a new medication (levetiracetam) and patient's current condition of thrombocytopenia as well as his previous diagnosis of vitamin B12 deficiency. To get to the bottom of the problem much faster, a systematic approach should have been adopted² as outlined in Table 1.

The pharmacist should have been more assertive in her method of enquiring about the swallowing problems of the patient because she had her suspicions right from the beginning. Perhaps explaining her reasons for asking would have helped to solve the problem much faster. She was never officially consulted on the problem, because the health care staff did not consider this to be a medication-related effect. This lack in communication should be addressed with a referral policy (see conclusions section below).

Was the treatment for osteoporosis appropriate?

Osteoporosis in men is much less well researched than in women. The World Health Organisation (WHO) criteria for osteoporosis and osteopenia are based on comparing a patient's bone mineral density (BMD) with that of a 25-year-old Caucasian female. The criteria were originally developed for women, but it is recognised that they can be appropriately applied to men.^{3,4} Some of the risk factors for osteoporotic fractures in men include: hypogonadism, corticosteroid use, family history, low body weight, smoking, and recurrent falls. Treatment for osteoporosis without conducting a BMD test may be considered if a patient presents with a fracture caused by minimal trauma.^{5,6}

On perusal of the medical notes from the GP surgery and the hospital, it became

clear that the diagnosis of osteoporosis or osteopenia had never been made. However, starting treatment seems appropriate because the patient had the following symptoms:

- Weight loss.
- Kyphosis.
- Back pain.
- Recurrent falls.

- Fractured clavicle on low impact. There was a possible investigation for vertebral fracture in 2002, but this is not confirmed.

Treatment of osteoporosis in men comprises lifestyle modifications, falls prevention and rehabilitation programmes, hip protectors and pharmacological interventions.⁶ Bone protective agents, such as bisphosphonates, are mainstay in the

Table 1. Assessment and management of adverse drug reactions (ADR)

Assess the nature and severity of the reaction

Several clinicians assessed the condition of the patient. It was not necessary to refer Mr B to hospital. At this point an adverse drug reaction (ADR) could have been suspected because of the acute onset of the symptoms.

Take a history of the presenting symptoms

Timing	Symptoms developed <ul style="list-style-type: none"> <input type="checkbox"/> 4 days after ibandronic acid administration <input type="checkbox"/> 5 days after first use of Fixodent® <input type="checkbox"/> 2 weeks after start of levetiracetam <input type="checkbox"/> 2 weeks after discontinuation of phenytoin
Relationship to dose	Symptoms improved over the next 2 weeks <ul style="list-style-type: none"> <input type="checkbox"/> Levetiracetam continued throughout <input type="checkbox"/> Ibandronic acid dosage interval monthly ?no further exposure <input type="checkbox"/> Fixodent® was discontinued
Other possible causes	Co-morbidities such as vitamin B12 deficiency and thrombocytopenia were investigated but ruled out <ul style="list-style-type: none"> <input type="checkbox"/> No access to herbal remedies <input type="checkbox"/> Fixodent® as OTC product <input type="checkbox"/> Drug-drug or drug-food interactions were not considered as cause

Consider the drug history and review any history of allergy or previous ADR

Drug history	Each drug should be scrutinised in terms of start date, dosage and interactions. OTC medication and herbal remedies should be taken into account.
Similar symptoms in the past	Similar symptoms were not reported in the notes, however, the patient is not a reliable source because of his degree of dementia.
Discontinued drugs	Phenytoin stopped two weeks ago ($t_{1/2} = 7-42$ hours)

Review the adverse effect profile of the drugs

Common sources for establishing ADRs are the *British National Formulary (BNF, www.bnf.org)*, the *electronic Medicine Compendium (eMC, www.medicines.org.uk)*, the Medicines and Healthcare products Regulatory Agency (MHRA, www.mhra.gov.uk), and local medicine information centres. Nearly all of the resources were explored with the following results:

- No reports for levetiracetam or Fixodent® according to manufacturers.
- Bisphosphonates very likely to cause serious injuries to mucosa if not taken properly, however there are no reports or images available to illustrate the effect after sucking and chewing of the tablets.

Consider further examination and investigation

This has not been necessary because of the nature of the ADR and improvement of the clinical condition.

Learning points

therapy of osteoporosis in men. They are usually given together with calcium and vitamin D supplements.^{6,7}

Alendronic acid (10mg once daily) is currently the only bisphosphonate licensed for the treatment of osteoporosis in men. It has been shown to reduce the incidence of vertebral fractures and to prevent a decrease in vertebral height.⁵ Preliminary data suggest that risedronate has positive effects on BMD and vertebral fracture rates in men.⁷ Other bisphosphonates have not been adequately evaluated.⁸

Ibandronic acid (Bonviva®) is a fairly new bisphosphonate licensed in 2005 for the treatment of postmenopausal osteoporosis. For this particular indication, it can be given as a single 150mg tablet once each month. There are currently no data for use in men available.

In summary, the treatment for osteoporosis was initially appropriate based on Mr B's clinical presentation. However, the choice of the bisphosphonate was inappropriate. A BMD test may not have been essential for starting treatment, but is useful for monitoring response to therapy.

Could the adverse effect have been prevented?

The patient's ability to follow the directions for administration needs to be taken into account. A patient with Mr B's degree of mental decline cannot report signs of oesophageal irritation, such as dysphagia or pain on swallowing. He should therefore be closely monitored by the nursing staff. One of the principles for prescribing in the

elderly is to choose a drug whose adverse effect profile is well documented as opposed to a new and relatively untested drug.⁸

Prescribing a fairly unknown drug has implications for the nursing staff. Although they must familiarise themselves with the medication they are administering, it became clear that in this instance they were not aware of the nature of ibandronate. The effect would have been seen more quickly with the common bisphosphonates, because they are administered weekly rather than monthly. In theory this may have led to ongoing mouth problems with very little time in between the doses to recover, but this would have prompted the staff to establish the cause.

Conclusion

There are a number of key messages arising from this case, which can be summarised as follows:

- improved communication between health care providers is needed
- implementation of a pharmacy referral policy for patients with swallowing difficulties will trigger an assessment as soon as problems arise
- identify and address learning needs
- educate health care staff about medication administration
- prescription of medicines with established efficacy and side-effect profile rather than 'black triangle' products is one of the principles of prescribing for elderly people
- arrange for regular review of medication if general condition and abilities for taking medication changes. The thres-



hold for medication reviews should be set fairly low. This can be incorporated into the pharmacy referral policy

- recommend adherence to administration directions and subsequently seeking advice from a pharmacist if deviation occurs. This can be part of a pharmacy referral policy. ✚

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Series editor: Duncan Petty, Consultant editor

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