Novel treatment (new drug/intervention; established drug/procedure in new situation)

Fentanyl – clarithromycin interaction

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Correspondence to Breda Cronnolly, Breda.Cronnolly@buckshealthcare.nhs.uk**Summary**

This case describes an incident where a patient with breast cancer and bone metastases, who was using a fentanyl patch, was started on a course of clarithromycin and experienced a respiratory arrest 2 days later. She was a hospital inpatient at the time and was treated with naloxone and the fentanyl patch was stopped at the time of the reaction. She recovered but was left without pain relief until seen in clinic by the palliative care consultant who restarted the fentanyl patch without further problems.

BACKGROUND

Having researched the information available on the fentanyl – clarithromycin interaction, the authors found that there was little information available and the information available was theoretical rather than being based on previous cases. Therefore, they decided to write this up to highlight the significance of the interaction and to highlight what alternatives were available to treat the patient should a similar case recur.

CASE PRESENTATION

A 72-year-old woman was admitted to hospital in June 2011 with a pleural effusion. She had a history of polycystic kidney disease and was on haemodialysis three times per week. She also had a history of breast cancer with bone and liver metastases and this caused some bone pain. She was applying fentanyl patches 87 µg/h 72 hourly, candesartan, doxazosin, zopiclone, amitriptyline, sevelamer, tamoxifen and dexamethasone. She also took paracetamol and ibuprofen when needed. On admission, her serum creatinine was raised at 393 µmol/litre and her urea was 6.8 mmol/litre. Her liver function tests were slightly raised (but not significantly); alkaline phosphatase was 158 µmol/litre.

As part of the treatment for the pleural effusion, the admitting clinician started a course of oral clarithromycin 500 mg 12 hourly on 7th June. The day after the clarithromycin was commenced, the patient attended dialysis and had a hypotensive event during the session. On the morning of 9th June she vomited and was very short of breath. During her physiotherapy session later in the morning, she reported feeling 'drugged', had slurred speech and felt very fatigued. When the patient was assessed by the registrar at lunchtime, he noted that she was in type 2 respiratory failure. Later in the day, a cardiac arrest call was put out as the patient was losing consciousness and had no respiratory effort. A dose of 200 µg of naloxone was given and the patient prescribed oxygen. Later on, an infusion of naloxone 4 mg/30 ml over 1 h was prescribed but this was stopped after 20 min as the patient became very restless and started twitching. She was given a dose of 1.5 mg haloperidol and this helped to settle her.

The clinician stopped the fentanyl patch suspecting that there was a possible interaction between the two

medicines. Fortunately at this time, the patient's pain was not an issue and the patient managed to control her pain on simple analgesics.

The day after the reaction, the patient reported feeling much better. She finished her course of antibiotics and was discharged home on 14 June.

She has since been restarted on the fentanyl patches for increasing pain without any recurrence of the respiratory failure.

DISCUSSION

Stockley's drug interactions¹ report a theoretical interaction between clarithromycin and fentanyl as no case reports have been found in the UK with this combination. There have been reports of similar interactions in Canada and the USA. A Canadian case study² describes a similar interaction between fentanyl patches and clarithromycin where a patient was treated with a fentanyl 200 µg patch and suffered a respiratory arrest 36 h after clarithromycin was started for *Helicobacter pylori* eradication. While our patient was on a lower dose, it should be born in mind that as she had chronic renal failure, her ability to metabolise both drugs would be reduced.

There is a report of erythromycin interacting with alfentanil as it increases the mean half life of alfentanil in some subjects. Erythromycin and clarithromycin both inhibit the cytochrome P450 isoenzyme CYP3A4 in the liver, which is involved in the metabolism of alfentanil, fentanyl and sufentanil.

Following this incident, we would recommend prescribers avoid using the two drugs concurrently wherever possible. In hindsight, doxycycline or azithromycin would be more appropriate antibiotics to treat this lady's infection. Azithromycin does not interact significantly with the cytochrome P450 system and is not believed to undergo the pharmacokinetic drug interactions seen with erythromycin and clarithromycin.³

It should also be noted that other drugs which are metabolised via the P450 system may interact with fentanyl patches and should be used with caution: such drugs include ritonavir, ketoconazole, itraconazole, troleandomycin, nelfinavir and nefazodone.

Learning points

- ▶ The clarithromycin-fentanyl interaction is a significant interaction and alternative antibiotics such as azithromycin or doxycycline would be more appropriate for patients using fentanyl patches.
- ▶ Azithromycin is not metabolised via the cytochrome P450 system and is therefore the safest macrolide to use in patients on interacting drugs.
- ▶ If analgesic medication needs to be stopped in patients who experience an interaction, consider alternative analgesia.

Competing interests None.

Patient consent Obtained.

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