Fatal interactions and reactions with colchicine: beware CYP3A4 inhibitors

Fluoroquinolone antibiotics and tendon disorders: still a problem

Drug-induced hyponatraemia

Please report all suspected reactions to these Drugs of Current Interest

- Atomoxetine (Strattera)
- Duloxetine (Cymbalta)
- Ezetimibe and simvastatin (Vytorin)
- Moxonidine (Physiotens)
- Paliperidone (Invega)
- Pramipexole (Sifrol)

- Pregabalin (Lyrica)
- Ranibizumab (Lucentis)
- Rosuvastatin (Crestor or Viacor)
- Sitagliptin (Januvia)
- Strontium ranelate (Protos)
- Varenicline (Champix)
1. Fatal interactions and reactions with colchicine: beware CYP3A4 inhibitors

Colchicine is indicated for the treatment of acute gout, but it has a narrow therapeutic index with significant potential for toxicity and severe drug interactions. In mid-2007, the TGA required updates to the Colgout and Lengout product information to limit colchicine usage to only where NSAID treatment is contraindicated, has failed or has caused unacceptable side effects; and to limit the maximum cumulative dose to 6 mg over 4 days in otherwise healthy adults (with washout intervals of at least 3 days if additional treatment is needed). Alternative treatments should be considered in the elderly and those with renal or hepatic impairment, but if colchicine is to be used in these patients, the cumulative dose should not exceed 3 mg over 4 days.

ADRAc has previously warned of the potential for severe or fatal toxicities with colchicine especially in overdose and in those with renal impairment. Toxic effects of greatest concern include blood dyscrasias due to bone marrow suppression, multi-organ failure and, more rarely, myopathy and rhabdomyolysis (which tend to occur in patients with impaired renal or hepatic function on long-term treatment with prophylactic doses of colchicine).

Since colchicine is metabolised mainly by CYP3A4, prescribers should be aware that drugs that inhibit this enzyme may increase blood colchicine concentrations and therefore increase the potential for colchicine toxicity. The CYP3A4 inhibitor, clarithromycin, was used concomitantly in 4 cases of severe colchicine toxicity reported to the TGA (see below), 3 of which described a fatal outcome. In one of the fatal cases, clarithromycin was being used as part of “triple therapy” for H pylori eradication in a patient undergoing treatment for gout with colchicine; this patient subsequently developed massive myelosuppression and multi-organ failure. Cases of fatal interactions between colchicine and clarithromycin have also been published.

To date, the TGA has received 243 reports for colchicine, including 53 describing blood dyscrasias such as neutropenia (15 reports), thrombocytopenia (10), pancytopenia (10), leukopenia (8) and agranulocytosis (4 reports), and an additional report describing sepsis and extensive severe maculopapular rash. Of these cases, 21 had not recovered at the time of reporting and 9 described a fatal outcome associated with renal failure, multi-organ failure or overwhelming sepsis. Colchicine was the sole suspected drug in 16 of the reports of blood dyscrasia but other drugs were also suspected in all of the reports that described a fatal outcome.

Prescribers are reminded that colchicine can be associated with significant toxicity and the risk-benefit should be considered on a case-by-case basis. In most cases, it should be used for short-term periods and only where NSAID therapy is contraindicated or has failed. Colchicine is best avoided if patients are taking drugs that inhibit CYP3A4 or have significant renal or hepatic impairment.

References:

2. Fluoroquinolone antibiotics and tendon disorders: still a problem

Tendon disorders – mainly tendinitis and tendon rupture – with fluoroquinolone antibiotics are well recognised and have featured in four previous Bulletins. In addition to fluoroquinolone use, increasing age and concomitant corticosteroids are established risk factors. Since the last alert in early 2006, we have received a further 23 reports of tendon disorder with fluoroquinolones, bringing the total to 183. Ten of the recent reports were submitted in the first half of 2008, indicating that this important and preventable adverse reaction continues to be a significant problem.

The fluoroquinolones are: ciprofloxacin (Arflox, C-Flox, Ciloxan, Cilooquin, Ciproxin, Ciprol, Profloxin, Proquin, Procip, Ciprobay, Ciaxone); norfloxacin (Insensye, Norflohexal, Noroxin, Nufloxib, Roxin); moxifloxacin (Avelox); as well as several other generic versions of ciprofloxacin and norfloxacin.

If a fluoroquinolone is prescribed, patients should be advised to stop the medicine at the first sign of tendon pain, swelling, or inflammation; if tendinitis is suspected, patients should avoid use of the affected area and promptly contact their doctor about changing to a non-fluoroquinolone antimicrobial drug.

The characteristics of the 23 reports received recently are similar to those reported in previous years. Thirteen describe Achilles tendinitis, 6 describe tendon rupture (3 of the shoulder or biceps, 3 of the Achilles) and 4 describe tendon pain and swelling. The majority involved patients (15 male, 4 female) aged over 56 years taking ciprofloxacin for 2-14 days, but disorders were also described in younger patients and in those taking a fluoroquinolone for > 1 month.

A fluoroquinolone (mainly ciprofloxacin) was the sole suspected medicine in 19 cases and concomitant prednisone was also suspected in 4 cases. In most cases, the reporter did not mention concomitant serious medical disorders other than that for which the antibiotic was indicated.

Recently, the TGA and other regulatory agencies including the FDA and Health Canada have reviewed the precautionary statements relating to this association in product information for the fluoroquinolones, and the FDA is considering introducing a boxed warning in product literature.5

References:

3. Drug-induced hyponatraemia

We continue to receive reports of hyponatraemia1 in association with various medicines. Severe hyponatraemia is a potentially devastating condition that can develop rapidly and without obvious prior symptoms, particularly in the elderly. Once severe hyponatraemia develops, specialist management is required to achieve a favourable outcome.2

Since May 2005 we have received 307 reports of hyponatraemia, several of which also described syndrome of inappropriate antidiuretic hormone secretion. 227 (74%) of the reports implicate a single drug as the suspected cause: mainly diuretics (126 reports) and antidepressants (78 reports, 33 of which were with an SSRI or SNRI).

Severe hyponatraemia (≤ 120 mmol/L), which can cause significant and permanent neurological injury or death1, was documented in 101 of the reports. Individual drugs most commonly associated with the severe form were hydrochlorothiazide (30 reports), indapamide (11), carbamazepine (8), paroxetine (8), venlafaxine (7) and sertraline (4).

Eighty of the 307 reports describe hyponatraemia in association with more than one agent; virtually all of these involved the combined use of a diuretic (hydrochlorothiazide or indapamide) with an ACE inhibitor or an angiotensin II receptor blocker or with an SSRI or SNRI. The combination of carbamazepine with an antihypertensive agent and a diuretic or with an antidepressant was also described.

Older age is generally acknowledged to be a risk factor for hyponatraemia. Two thirds of the reports received since 2005 describe patients aged over 70 years and over 70% involved women. Onset of hyponatraemia occurred within the first month in 74% of cases that provided this information (median, 11 days).

The clinical presentation varied greatly but the most commonly described disorders were: neurological (including convulsions, postural hypotension, syncope, altered consciousness or coma, somnolence, headache, ataxia, tremor, abnormal gait, visual disturbances and cerebral oedema), psychiatric (including confusion, delirium, agitation and hallucinations) and gastrointestinal (including anorexia, nausea and vomiting). Most reports (162) documented recovery; 56 had not recovered and the outcome was unknown for 61 at the time of reporting.

This series of reports included 2 deaths which were considered attributable to hyponatraemia.
Although a few reports described hyponatraemia as an incidental finding on routine laboratory testing in asymptomatic patients, there is evidence that even mild levels of chronic hyponatraemia may contribute to an increased rate of falls. In fact, 9 falls were documented in this series of reports.

ADRAC reminds prescribers that electrolyte monitoring should be done often and early in patients with risk factors for developing hyponatraemia, including the elderly (particularly if diarrhoea is present) and those on diuretics, SSRIs or SNRIs, carbamazepine or any combination of these.

References:

WHAT TO REPORT? (you do not need to be certain, just suspicious!)

ADRAc encourages the reporting of all suspected adverse reactions to medicines, including vaccines, OTC medicines, herbal, traditional or alternative remedies. ADRAC particularly requests reports of:

*ALL suspected reactions to new drugs (see drugs of current interest, front page)
*ALL suspected drug interactions
*Suspected reactions causing
  •Death
  •Admission to hospital or prolongation of hospitalisation
  •Increased investigations or treatment
  •Birth defects

For blue cards
Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the website: [http://www.tga.gov.au/adr/bluecard.pdf](http://www.tga.gov.au/adr/bluecard.pdf) or from the Adverse Drug Reactions Unit ☎ 02-6232-8744.

Reports can also be submitted electronically, by going to the TGA website [http://www.tga.gov.au](http://www.tga.gov.au) and clicking on "report problems" on the left, by fax: 02-6232-8392, or email: ADR.Reports@tga.gov.au

ISSN 0812-3837 © Commonwealth of Australia 2008


All correspondence to be addressed to: The Secretary, ADRAC, PO Box 100, Woden, ACT, 2606