

these cases should be classified as 'acute' and 'tardive' Pisa syndrome.

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## Self-poisoning with Pet Medications

**To the Editor:** Many pet medications are pharmacologically similar to those prescribed for human use. We describe a case in which a pet's antiepileptic drug (phenobarbitone) was deliberately used for self-poisoning. To our knowledge, this is the first known instance of a deliberate self-poisoning utilizing pet medication.

A 55-year-old woman with no significant past medical history, apart from depression, on no medications, was found unresponsive at home by her husband. Upon arrival to the hospital, her vital signs were normal and physical examination was unremarkable except for a reduced consciousness level with a Glasgow coma scale of 9/15. Initial investigations, including full blood count, renal and liver functions, arterial blood gas (ABG), electrocardiography (ECG) and chest x-ray, were normal. Computed tomography (CT) scan of the brain was also normal.

On the second day, an empty bottle of phenobarbitone, prescribed for her epileptic dog, was found at home by the husband. Toxicology screen revealed a serum phenobarbitone level of 76 mg/L, confirming the diagnosis of phenobarbitone overdose. Four days later, she made a full recovery and admitted taking 60 tablets (1.8 g) of her dog's phenobarbitone. She was discharged to an outpatient psychiatric service 6 days post admission. Phenobarbital is the initial drug of choice for managing idiopathic epilepsy in dogs and cats.<sup>1</sup> It may also be used to treat seizures in horses when benzodiazepine treatment has failed or is contraindicated. Obtaining a pet medical history may provide critical information in the assessment of patients with a suspected overdose.

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## Life-threatening, Multiple Hypersensitivity Reactions Induced by Rifampicin in One Patient with Pulmonary Tuberculosis

**To the Editor:** Rifampicin (RFP) is one of the most effective antibiotics available for the treatment of tuberculosis. Its best known side effect is liver toxicity. Fewer than 4% of patients have immunoallergic reactions such as rash, fever, nausea, and vomiting.<sup>1</sup> More severe hypersensitivity reactions are uncommon and occur in cases of intermittent regimens, high-dose administration, prior treatment with RFP, or HIV infection.<sup>2</sup> We report one such case in a patient without HIV infection.

A 35-year-old man of North African ethnicity was diagnosed with pulmonary tuberculosis and was started on RFP, isoniazid (INH), pyrazinamide (PZA), and ethambutol (EB) at the usual daily doses. After three weeks of continuous therapy, he was admitted to another hospital with fever, vomiting, diarrhea, and oliguria. Creatinine was 8.6 mg/dL (normal values 0.4-1.5), urea nitrogen 80 mg/dL (15-50), and leukocytes were  $24.7 \times 10^9/L$  ( $4-11 \times 10^9/L$ ); the remaining biochemical and hematological parameters were normal. All antituberculous drugs were stopped at that time. Clinical conditions and renal function improved following hemodialysis and supportive therapy. Two months later, the patient was admitted to our hospital with fever (38.6°C), cough, dyspnea, blood pressure 110/70 mmHg, heart rate 108 beats/min, and oxygen saturation on room air of 96%. Crackles were present over the left pulmonary upper lobe. Acid-fast bacilli were detected in the sputum. RFP, INH, PZA, EB were prescribed. Two hours after taking the first pill of RFP (600 mg), the patient developed vomiting, myalgia, abdominal pain, confusion, dyspnea, fever (39°C), hypotension (70/30 mm Hg), erythematous rash involving the face and thorax, and peripheral cyanosis. The main laboratory features are summarized in the Table. Hypersensitivity reaction included anaphylactic shock, liver injury, hemolytic anemia, acute renal failure and disseminated intravascular coagulation (DIC). Urinalysis showed hemoglobinuria, albuminuria, rare white and red cells. Serum IgE was within normal limits and anti-RFP IgE antibodies were negative by radioallergosorbent test. Direct and indirect antiglobulin (Coombs) tests were positive. RFP-dependent IgG and IgM antibodies with complement fixing capability were present in the serum.<sup>3</sup> The patient was transferred to the intensive care unit (ICU) and underwent hemodialysis. No further hemolysis occurred one week after RFP was stopped, and hemodialysis was discontinued three weeks after the onset of adverse

**Table. Main laboratory features of the patient (time 0 indicates rifampicin re-exposure)**

| Parameter<br>(normal values)                              | At hospital<br>admission   | 2 hours following the<br>first dose of RFP | 7 days after the<br>first dose of RFP | 21 days after the<br>first dose of RFP |
|-----------------------------------------------------------|----------------------------|--------------------------------------------|---------------------------------------|----------------------------------------|
| Hemoglobin (12–16 $\mu\text{mol/l}$ )                     | 13.2 $\mu\text{mol/l}$     | 7.9 $\mu\text{mol/l}$                      | 8.6 $\mu\text{mol/l}$                 | 9.3 $\mu\text{mol/l}$                  |
| Leukocyte count ( $4\text{--}10 \times 10^9/\text{l}$ )   | $7.6 \times 10^9/\text{l}$ | $28.3 \times 10^9/\text{l}$                | $14.4 \times 10^9/\text{l}$           | $6.2 \times 10^9/\text{l}$             |
| Platelet count ( $140\text{--}440 \times 10^9/\text{l}$ ) | $287 \times 10^9/\text{l}$ | $76 \times 10^9/\text{l}$                  | $146 \times 10^9/\text{l}$            | $300 \times 10^9/\text{l}$             |
| Creatinine (0.4–1.5 mg/dL)                                | 1.15 mg/dL                 | 3.9 mg/dL                                  | 8.5 mg/dL                             | 6.7 mg/dL                              |
| BUN (15–50 mg/dL)                                         | 52 mg/dL                   | 75 mg/dL                                   | 160 mg/dL                             | 120 mg/dL                              |
| AST (5–10 U/L)                                            | 42 U/L                     | 916 U/L                                    | 22 U/L                                | 33 U/L                                 |
| ALT (5–40 U/L)                                            | 42 U/L                     | 290 U/L                                    | 56 U/L                                | 12 U/L                                 |
| Total bilirubin (0.30–1.00 mg/dL)                         | 0.72 mg/dL                 | 6.82 mg/dL                                 | 1.00 mg/dL                            | 0.48 mg/dL                             |
| Direct bilirubin (0.10–0.30 mg/dL)                        | 0.29 mg/dL                 | 2.56 mg/dL                                 | 0.46 mg/dL                            | 0.22 mg/dL                             |
| INR (<1.17)                                               | ND <sup>a</sup>            | 4.98                                       | 0.98                                  | 0.96                                   |
| APTT (<1.16 sec)                                          | ND <sup>a</sup>            | 171.9                                      | 31.7                                  | 33.8                                   |
| Fibrinogen (150–400 mg/dL)                                | ND <sup>a</sup>            | 103 mg/dL                                  | 611 mg/dL                             | 520 mg/dL                              |
| D-Dimer (<0.5 $\mu\text{g/ml}$ )                          | ND                         | 90 $\mu\text{g/ml}$                        | 3.2 $\mu\text{g/ml}$                  | 1.97 $\mu\text{g/ml}$                  |

RFP, rifampicin; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; APTT, activated partial thromboplastin time; ND, not determined.

events. Clinical recovery and return of laboratory data to normal values occurred over a 5-week period. The patient was subsequently treated with INH, PZA, EB, ciprofloxacin, and recovered from tuberculosis.

Renal toxicity of RFP has been reported sporadically. Acute renal failure (ARF) is the most common presentation and typically develops during intermittent regimens or on reintroduction of the drug. Among 12 patients who underwent kidney biopsy in a series of 25 consecutive patients with RFP-associated acute renal failure, 7 patients (58%) had interstitial nephritis with acute tubular necrosis. The onset occurred with gastrointestinal, flu-like symptoms, and oliguria; anemia and thrombocytopenia each occurred in 60% of patients. All patients regained normal renal function.<sup>4</sup> ARF following reinstitution of RFP usually takes the form of interstitial nephritis, which may be associated with hemolysis and hemoglobinuria.<sup>5</sup> In almost all reported cases of acute interstitial nephritis, anti-rifampicin antibodies (mainly IgM and IgG) were found, the most likely pathogenesis being adhesion of immune complexes to renal tubular epithelium and complement binding.<sup>2</sup> Our finding of RFP-dependent IgG and IgM serum an-

tibodies with complement fixing capability indicated that hemolysis in our patient can be attributed to RFP. DIC and thrombocytopenia were also likely due to an antigen-antibody reaction with complement activation and hemolysis. These adverse reactions related to immune complexes usually regress after discontinuation of the drug and supportive therapy,<sup>2,5</sup> as in our case. In addition, our patient developed rash, anaphylactic shock, and liver injury. Although drug-associated anaphylactic reactions may be due to a nonimmunologically mediated release of histamine from basophils, these events are usually consistent with the IgE-mediated, immediate type of hypersensitivity. IgE antibodies to RFP have been detected in some patients with anaphylactic reactions to RFP, but were negative in our patient. In addition, several cases of anaphylactic reactions have been published in which intradermal tests with RFP were negative. Hence, available serologic and cutaneous tests can fail to predict anaphylactic reactions to RFP.<sup>2</sup> To our knowledge, only five cases of coincidental flu-like and anaphylactic shock episodes induced by RFP have been reported so far. Besides these reactions, our patient also had ARF and DIC, and thus he experienced most of

the possible hypersensitivity reactions to RFP. In conclusion, rechallenge with rifampicin can cause more serious hypersensitivity reactions and must be avoided after both anaphylactic reactions and nonlife-threatening adverse events caused by immune complexes, such as ARF.

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## Treating Osteoarthritis in the Elderly: Should Recent Data on NSAIDs Change Our Way of Practice?

**To the Editor:** Osteoarthritis (OA) is one of the leading causes of chronic disability in the elderly, predominantly because of involvement of the knee and hip joints. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used to reduce pain and inflammation and improve function in OA patients. We have been aware of side effects of NSAIDs including renal and gastrointestinal toxicity for years. Recently, a few studies<sup>1-3</sup> have suggested that besides COX-2 inhibitors, some nonselective NSAIDs could also raise the relative risk of cardiovascular adverse events, such as acute myocardial infarction (MI). This warrants that we take a fresh look at NSAID use and their safety in the elderly.

A recent meta-analysis of 14 observational studies from population databases between January 1980 to June 2005 compared the risk of acute MI in NSAID users with that in non- or remote NSAID users.<sup>1</sup> Nonselective NSAIDs as a class were found to be associated with an increased acute MI risk [relative AMI risk 1.19; 95% CI 1.08 to 1.31]. Similar findings were found with diclofenac [relative AMI risk 1.38; 95% CI 1.22 to 1.57] and ibuprofen [relative AMI risk 1.11; 95% CI 1.06 to 1.17]. However, this effect was not observed with naproxen [relative AMI risk 0.99; 95% CI 0.88 to 1.11].

In a population-based, nested case-control analysis by Hippisley-Cox and Coupland,<sup>2</sup> the risk of acute MI was compared between patients taking COX-2 inhibitors and nonselective NSAIDs. Data

was obtained from 367 general practices contributing to the UK QRESEARCH database between 2000 and 2004. Subjects included 9218 patients with a first ever diagnosis of acute MI during the four-year study period and 86,349 controls matched for age, calendar year, sex, and practice. Despite making adjustments for many potential confounders such as smoking status, comorbidities, use of statins, aspirin, and antidepressants, a significantly increased risk of acute MI was found to be associated with current use of diclofenac (1.55, 1.39-1.72); ibuprofen (1.24, 1.11-1.39) and rofecoxib (adjusted odds ratio 1.32, 95% confidence interval 1.09-1.61), compared with no use within the previous three years.

Gislason et al<sup>3</sup> reported that selective COX-2 inhibitors in all dosages and nonselective NSAIDs in high dosages increase mortality in patients with a previous MI. Of 71,515 patients hospitalized with first-time acute MI during 1995 to 2002, 58,432 (81.7%) were alive at discharge and were included in this study. All prescription claims for NSAIDs and COX-2 inhibitors after discharge were identified from nationwide Danish administrative registers. The risk of death and rehospitalization for acute MI was studied with the use of multivariable proportional hazards models and case-crossover analysis. It was found that 9,773 patients experienced rehospitalization for MI, and 16,573 died. They found an increased risk of death with any use of ibuprofen, diclofenac, other NSAIDs, rofecoxib and celecoxib. The hazard ratios and 95% confidence intervals for death were 2.80 (2.41-3.25 for rofecoxib), 2.57 (2.15-3.08 for celecoxib), 2.40 (2.09-2.80 for diclofenac), 1.50 (1.36-1.67 for ibuprofen), and 1.29 (1.16-1.43 for other NSAIDs). There were trends for increased risk of rehospitalization for acute MI associated with the use of both the selective COX-2 inhibitors and the nonselective NSAIDs. The duration of treatment was similar with rofecoxib, celecoxib, and ibuprofen, at 37

to 40 days, but the duration of treatment was only 20 days for diclofenac and 83 days for other NSAIDs. A clear dose-related response in the increased risk of death for both coxibs and NSAIDs was seen, although a similar association was not found for risk of recurrent MI.

In a nutshell, we should be more cautious when prescribing NSAIDs to elderly patients with OA who have known cardiovascular disease or several risk factors for the same. Patients need to be involved in the decision-making process while being informed of the potential risks of NSAIDs and alternative choices. In the elderly, when NSAIDs are being used in patients with risk factors for cardiovascular disease, it would be prudent to limit their dose to the lower part of the effective range; eg, limiting diclofenac to 100 mg/d, ibuprofen to 1200 mg/d, and naproxen to 500 mg/d. This dose may further need to be adjusted based on the patient's creatinine clearance. Adding misoprostol or a proton pump inhibitor may reduce their GI side effects. However, in patients with known coronary artery disease or with a past history of stroke, even these doses could cause potential harm, and for now, it would be best to avoid NSAIDs in this particular group of patients, until more conclusive evidence becomes available.

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