

# LETTERS AND COMMENTS

## Agranulocytosis associated with nitrofurantoin therapy

TO THE EDITOR: Nitrofurantoin was introduced in 1953 for treatment of gram-positive and gram-negative pathogens common to the genitourinary tract. Hematologic reactions associated with nitrofurantoin are considered rare.<sup>1,2</sup> We describe a case of agranulocytosis associated with a short course of nitrofurantoin.

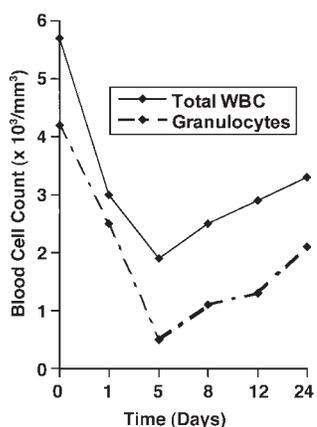
**Case Report.** A 74-year-old white man in long-term care complained of right lower-quadrant pain and urinary retention. Vital signs upon examination were BP 118/62 mm Hg, pulse 93 beats/min, respiratory rate 24 breaths/min, and temperature 37.7 °C. Urine culture and sensitivity test reported methicillin-sensitive *Staphylococcus aureus*. The patient did not exhibit renal insufficiency, with estimated creatinine clearance 64 mL/min.

The patient was diagnosed with a urinary tract infection and treated with nitrofurantoin 100 mg 4 times a day. Baseline blood cell count 2 months earlier had shown a total white blood cell (WBC) count of  $5.7 \times 10^3/\text{mm}^3$  and granulocyte count of  $4.2 \times 10^3/\text{mm}^3$ . On the fifth day of nitrofurantoin therapy, total WBC and granulocyte counts decreased to  $1.9 \times 10^3/\text{mm}^3$  and  $0.5 \times 10^3/\text{mm}^3$ , respectively (Figure 1). No signs of hypotension or allergic reaction were illustrated upon examination of the patient.

Nitrofurantoin was discontinued after 5 days of therapy and replaced with cefuroxime. Two days following discontinuation of nitrofurantoin, the total WBC and granulocyte counts increased to  $2.5 \times 10^3/\text{mm}^3$  and  $1.1 \times 10^3/\text{mm}^3$ , respectively (Figure 1). Twenty days later, the total WBC and granulocyte counts continued to improve. The Naranjo probability scale showed a probable relationship between agranulocytosis and nitrofurantoin.<sup>3</sup>

**Discussion.** According to worldwide adverse drug reaction data, approximately 0.0004% of nitrofurantoin treatments have resulted in hematologic reactions.<sup>1</sup> In an evaluation of 921 patients, 20 patients presented with blood dyscrasias associated with nitrofurantoin. None of those patients demonstrated renal insufficiency associated with nitrofurantoin. Two of the 20 cases resulted in fatal agranulocytosis associated with nitrofurantoin, but a second drug was a contributing factor (sulfamerazine, sulfaproxyline, levomepromazin).<sup>2</sup> Another case of fatal nitrofurantoin-induced agranulocytosis involved a 14-year-old black female with systemic lupus erythematosus and renal failure.<sup>4</sup> In one case, recurrent agranulocytosis occurred after a short course of nitrofurantoin 150 mg/day.<sup>5</sup> The 62-year-old woman was rechallenged, and agranulocytosis developed within 3 days. The patient recovered after discontinuation of nitrofurantoin.

In comparing these cases, agranulocytosis seemed to occur independently of renal function, but creatinine clearance <60 mL/min would be a risk factor.<sup>2,5</sup> Due to our patient's short course of therapy and adequate



**Figure 1.** Changes in the total white blood cell (WBC) and granulocyte counts with nitrofurantoin-associated agranulocytosis.

renal function, agranulocytosis induced by nitrofurantoin may favor an immunologic reaction rather than a toxic effect as the pathogenetic mechanism. However, accumulation may still play a role in the development of agranulocytosis.<sup>2,4,5</sup>

Most studies report nitrofurantoin as a treatment option for urinary tract infections; it is well tolerated and has a relatively low risk of adverse effects. According to the literature, agranulocytosis rarely occurs, but still needs to be considered as a possible adverse effect.<sup>1,2</sup> Monitoring the total WBC, granulocyte count, and renal function may prevent agranulocytosis in patients treated with nitrofurantoin.

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## Death of twins after intravenous varicella zoster immunoglobulin

TO THE EDITOR: "Immunization Against Infectious Disease" recommends that varicella zoster immunoglobulin (VZIG) be given intramuscularly—never intravenously.<sup>1</sup> However, intravenous VZIG preparations are available, and their safety and efficacy have been documented.<sup>2</sup> We report on twins who developed pulmonary hemorrhage and died after receiving intravenous VZIG.

**Case Report.** Male twins (gestational age 33 wk), weighing 2.05 and 2.45 kg (diamniotic, dichorionic placenta), were born to a primigravida mother who had developed varicella zoster 5 days previously. Both had respiratory distress soon after birth, needing continuous positive-airway pressure ventilation. X-ray at 2 hours was suggestive of wet lungs. Both infants received vitamin K (menaphthone sodium bisulphate, 1 mg intramuscularly).

In the presence of maternal varicella, they were prescribed injectable acyclovir 10 mg/kg/dose every 8 hours, diluted in distilled water and given over 30 minutes, starting at 4 hours of life. Additionally, both babies were administered 125 units (5 mL) of intravenous VZIG (Varitect CP, Biotest Pharma GmbH, D-63303 Dreieich, Germany, Lot 155011) starting at 8 hours of life. The VZIG was diluted in 10 mL of distilled water (total volume 15 mL), and 0.2 mL of this solution was given over

10 minutes (sensitization dose). Subsequently, in accordance with the product manual information, as their vital signs, heart rate, respiratory rate, and oxygen saturation were stable, the infusion rate was increased to 5 mL/h. The infusion continued for 3 hours, and the infants' vital signs recorded on the saturation monitor were normal throughout infusion. However, 15 minutes later, the first of the twins started gasping. Heart sounds were not audible. On intubation, fresh blood was seen pouring out of the airway. Five minutes later, the second twin also had cardiorespiratory arrest and pulmonary hemorrhage. Neither baby could be revived.

**Discussion.** The Naranjo probability scale suggests that intravenous VZIG was the possible cause of death of the twins.<sup>3</sup> The same adverse reaction occurring in twins exposed to a drug is in some ways akin to the recurrence of symptoms in an individual on rechallenge with the drug. The Naranjo scoring system does not anticipate this possibility, and no additional points on the scale have been allotted for this rare occurrence.

The manufacturer confirmed that there have been no previous reports of similar problems. As of November 17, 2004, our report is arguably the first of fatal adverse effects from the intravenous preparation.

Anaphylactoid reactions, immunoglobulin (Ig) A-mediated antibody reaction in IgA-deficient twins, or toxin-related alveolar damage could have been responsible for their deaths. In the absence of adverse effects in other patients who had used VZIG from the same lot, toxin contamination is unlikely. IgA sensitization and an anaphylactoid reaction seem unlikely at this age.

Transfusion-related acute lung injury (TRALI) is another possibility. It is due to a reaction between donor leukoagglutinating or human leukocyte antigen-specific antibodies and the recipient's white blood cells, causing damage to pulmonary vasculature.<sup>4</sup> Many blood products are implicated in TRALI. It has been reported in a neonate receiving granulocyte transfusion<sup>4</sup> and in an adult following administration of IVIG.<sup>5</sup> While newborns seldom develop anaphylactoid reactions to blood products, transfusion-related lung reactions may occur.

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#### Bleeding associated with indapamide SR therapy

TO THE EDITOR: Indapamide is a commonly prescribed thiazide-like diuretic that has been approved for treatment of hypertension. It is well tol-

erated and generally considered safe. In accordance with international recommendations on the need to decrease doses of antihypertensive drugs and diuretics in first-line therapy of hypertension, a low-dose (1.5 mg) sustained-release (SR) formulation of indapamide was developed to optimize the drug's efficacy/safety ratio.<sup>1</sup> Indapamide SR is associated with a decreased risk of adverse reactions. We present a case of mucosal bleeding related to indapamide SR therapy.

**Case Report.** A 58-year-old woman with a 10-year history of moderate hypertension was taking indapamide SR 1.5 mg/day. Other medications or herbal products were not administered. About 18 months after starting indapamide SR treatment, she experienced bleeding from the mucous membrane of the tongue.

Blood chemistries revealed mild thrombocytopenia (hemoglobin 13 g/dL, erythrocytes  $4.21 \times 10^6/\text{mm}^3$ , leukocytes  $5.5 \times 10^3/\text{mm}^3$ , platelets  $132 \times 10^3/\text{mm}^3$ , normal differential cell count). Erythrocyte sedimentation rate was 20 mm/h. Until that time, the patient's hematologic parameters had been unremarkable. She had no family or personal history of congenital bleeding diathesis, and no history of liver disease or blood transfusion. Physical examination revealed only petechiae affecting the upper extremities and anterior chest. There was no lymphadenopathy or hepatosplenomegaly.

The monotherapy suggested indapamide SR as the cause of bleeding in this patient. Treatment was discontinued immediately, and propranolol 80 mg/day was initiated. Bleeding stopped promptly after cessation of indapamide SR therapy. The platelet count rose to a normal level ( $250 \times 10^3/\text{mm}^3$ ) 10 days after withdrawal of indapamide SR, without further treatment of bleeding. The skin lesions on the woman's anterior chest faded quickly and resolved completely within 2 weeks. Given the serious nature of the bleeding, we decided not to reinstate indapamide SR. The Naranjo probability scale indicated a probable relationship between indapamide SR and mucosal bleeding.<sup>2</sup>

**Discussion.** To our knowledge, as of November 28, 2004, this is the first report of indapamide SR causing mucosal bleeding. No additional cases of bleeding with indapamide SR were available from the manufacturer (Laboratoires Servier).

Theoretically, the possible mechanism of the effect of indapamide on vascular-platelet hemostasis may be its antiaggregating property, which could contribute to normalizing the hyperresponsiveness of platelets from hypertensive patients. Indapamide inhibited the second wave of adenosine diphosphate-induced aggregation and inhibited collagen-induced aggregation of platelet-rich plasma by 50% in vitro.<sup>3</sup> Indapamide also can suppress the production of thromboxane A<sub>2</sub>.<sup>4</sup> Indapamide added to standard antihypertensive treatment has led to a decrease of platelet aggregation in hypertensive patients.<sup>5</sup>

This case report posits indapamide SR as a likely cause of mucosal bleeding and alerts clinicians to the possibility of this additional complication with indapamide SR. Since the frequency of this adverse effect is not known, it may be difficult at present to recommend routine platelet count monitoring for this complication. However, prescribers should be aware that bleeding may occur in patients who receive a high cumulative dose during long-term treatment.

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### Interaction between tadalafil and itraconazole

TO THE EDITOR: Erectile dysfunction (ED) is a common medical condition affecting millions of men worldwide.<sup>1</sup> Sildenafil citrate, an inhibitor of phosphodiesterase type-5 enzyme (PDE5), is the first and most widely prescribed oral agent for ED. Tadalafil and vardenafil are newer PDE5 inhibitors approved for marketing. We describe priapism and increased duration of tadalafil action in a patient treated for ED in addition to itraconazole for onychomycosis.

**Case Report.** A 56-year-old white man with no concomitant illness had been using sildenafil 100 mg as needed for ED from 1999 to April 2003 without any known adverse events. He then switched to tadalafil 10 mg, hoping to achieve better and longer efficacy. He was not taking other drugs and did not complain of any undesirable effects. In September 2003, because of recurrent onychomycosis of the foot, he was prescribed itraconazole 400 mg/day for 7 days monthly. He had previously taken itraconazole, even while taking sildenafil, without experiencing adverse effects.

During the first day of monthly (October) itraconazole therapy, the patient took tadalafil. Within a few hours, priapism occurred, lasting >4 hours, without impediment of urinary flow. In November (still during itraconazole weekly treatment), the patient took the same dose of tadalafil and the same symptom occurred, with analogous onset and duration. This time he reported the reaction to his physician, adding that painful erections had occurred repeatedly over 72 hours. During the following 7 months, the patient did not use tadalafil, and the adverse effect did not recur when he resumed use of sildenafil during itraconazole therapy.

**Discussion.** As of November 19, 2004, priapism has not been associated with tadalafil.<sup>2,3</sup> Tadalafil is primarily metabolized through CYP3A4. Ketoconazole, a CYP3A4 inhibitor, at doses of 200 mg/day has increased tadalafil (10 mg) AUC and maximum concentration 2 times and 15%, respectively, relative to the values of the same dose of tadalafil alone.<sup>3</sup> Therefore, although no studies of possible interaction have been performed, caution is required when tadalafil is given with other potent CYP3A4 inhibitors, such as itraconazole.

In our patient, the tadalafil-itraconazole interaction, leading to priapism, was confirmed by positive rechallenge, absence of concomitant medications and conditions and by the absence of adverse effects with tadalafil alone. Based on the Naranjo probability scale, the event/drug relationship was probable.<sup>4</sup>

Surprisingly, this adverse effect never occurred in the patient during concurrent use of itraconazole and sildenafil, which is a substrate not only of CYP3A4 but also of CYP2C9. Furthermore, one sildenafil circulating metabolite may contribute to approximately 20% of the net pharmacologic effect of the drug.<sup>5</sup> On the contrary, the tadalafil main metabolite is 13 000 times less potent than tadalafil.<sup>3</sup>

In the absence of other observations, we assume that the pharmacokinetic interaction between tadalafil and itraconazole could have produced priapism in our patient. To our knowledge, this is the first report of a tadalafil-itraconazole interaction leading to priapism; this case indicates that prescribers should monitor tadalafil closely for the risk of drug interactions.

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### Aripiprazole-associated dyskinesia

TO THE EDITOR: Aripiprazole, a dopamine-2 (D<sub>2</sub>) receptor partial agonist, has been associated with a placebo-level incidence of extrapyramidal symptoms and treatment-emergent dyskinesia.<sup>1</sup> The incidence of dyskinesia is similar to that reported for risperidone and olanzapine.<sup>2</sup> One case report documented improvement of antipsychotic-induced tardive dyskinesia with aripiprazole<sup>3</sup>; it has not been documented to produce de novo dyskinesias. We report a case of new-onset aripiprazole-associated lingual dyskinesia.

**Case Report.** A 35-year-old man had a 22-year history of schizoaffective disorder that had been largely untreated. He had minimal intermittent antipsychotic exposure prior to admission to our hospital. Medication history included less than one-month trials of desipramine, fluoxetine, sertraline, olanzapine, and trifluoperazine at various times, with no reported movement disorder symptoms. His medical history was noncontributory; he had never undergone neuroimaging. He had not taken any antipsychotics for 5 months prior to or 4 months after hospital admission for acute psychotic exacerbation (July 2003).

On November 25, 2003 (day 1), abnormal movements were absent, and oral olanzapine 5 mg was initiated. The dose was increased to 10 mg daily on day 15 due to persistent symptoms. The patient's total Abnormal Involuntary Movement Scale (AIMS) score on day 10 was zero. After one month, he requested a medication change due to concern over weight gain; therefore, on day 34, aripiprazole was started at 10 mg/day. The aripiprazole dose was increased to 20 mg/day on day 55 due to continued psychosis, and olanzapine was discontinued.

On day 105, after 7 weeks of monotherapy with aripiprazole, the patient reported that his tongue felt large, slow, thick, and uncoordinated. These symptoms had emerged over a few days; he was noted to be talking with a lisp. The dyskinesia of his tongue manifested as rolling/writhing movements, exacerbated by purposeful movements (eg, finger tapping), and interfered with his sleep. He experienced episodic quivering of the upper lip; examination did not detect any other dyskinesic movements. The AIMS total score on day 105 was 8. Aripiprazole was discontinued and, within a day, the patient noted mild improvement. Within 10 days (day 115), the dyskinesia had resolved and the AIMS score on day 127 was zero. At the time of writing, the patient remained hospitalized. He was subsequently titrated onto quetiapine 500 mg/day and, after 2 months of therapy, had no recurrence of lingual dyskinesia.

**Discussion.** This report describes the emergence of lingual dyskinesia with aripiprazole monotherapy. The absence of abnormal movements before starting this agent, the lack of concurrent therapy, and prompt resolution upon drug discontinuation suggest that aripiprazole may have produced the abnormal movements. The Naranjo probability scale indicated a probable relationship.<sup>4</sup> It is doubtful that this reaction represented withdrawal dyskinesia given the short, low-dose olanzapine trial prior to aripiprazole, and the dyskinesia did not emerge until many weeks after olanzapine was discontinued. The patient's history of intermittent antipsychotic exposure, albeit limited, may have rendered him vulnerable to dyskinesias. It is notable that he did not experience similar symptoms in the setting of treatment with D<sub>2</sub> receptor antagonists. This suggests

that aripiprazole's partial agonist action may precipitate dyskinetic movements similar to those seen with full dopamine agonists in vulnerable individuals.<sup>5</sup>

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#### Diazepam-associated gynecomastia

TO THE EDITOR: Drug-induced gynecomastia in men is thought to result from an altered ratio between testosterone and estrogen concentrations.<sup>1</sup> However, in many cases, the mechanism of drug-induced gynecomastia remains unclear. Benzodiazepines is one class of medications implicated in causing drug-induced gynecomastia. Among case reports of benzodiazepine-induced gynecomastia, diazepam, which can modify estradiol levels, is most often responsible.<sup>2,3</sup> In our practice, we encountered one such case.

**Case Report.** A 47-year-old man presented with breast enlargement that became apparent 2 months earlier. He had begun taking diazepam about 10 months prior to our interview, self-medicating for nervousness and anxiety. (Diazepam is available without prescription in Serbia.) He started with diazepam 5–10 mg, taking it occasionally. He was not satisfied with the expected effects, and increased the dose to 10–30 mg/day. Two weeks before our meeting, he dramatically increased the diazepam dosage to 40–50 mg/day. Notably, he denied being sedated or feeling tired. Just the opposite, he mentioned becoming aggressive and more nervous which, in his opinion, required further increases of the dose.

During the last few months of diazepam treatment, the patient's breasts had become gradually enlarged (measured at 10.6 cm in width, 2.7 cm above the middle line of the chest), with no secretion or nodes. This enlargement could have been due to a weight increase: he was notably obese (body mass index [BMI] 32.19 kg/m<sup>2</sup>), and he attributed the breast enlargement to his obesity. Besides diazepam, the man denied the use of other medications except cotrimoxazole on one occasion >6 months before his presentation. He had no other medical diagnoses.

Three weeks after we advised the patient to decrease his diazepam intake gradually, he took the drug only occasionally at a dose of 5–15 mg/day. This resulted in a large breast dimension reduction, reaching near normal size (measured at 7.2 cm in width, 1.6 cm above the middle line of the chest). During this time, his BMI decreased slightly, to 31.2 kg/m<sup>2</sup>. He also noticed that he was less nervous and aggressive. According to the Naranjo probability scale, the likelihood of the patient's gynecomastia being due to the diazepam was possible.<sup>4</sup>

**Discussion.** Self-medication has risks and benefits. Correct patient understanding of the proper use, expected effects, and possible adverse effects are very important. In our patient, misunderstanding of the proper dose and adverse effects resulted in overuse of diazepam, which led to the development of gynecomastia, as well as nervousness, anxiety, and toler-

ance. All adverse effects showed regression after diazepam consumption was gradually decreased. Special attention should be paid to obese patients, where diazepam-induced gynecomastia can be misdiagnosed.

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#### Correction: long-acting injectable risperidone

The following wording replaces the last 2 sentences of the first paragraph under Clinical Trials in the December 2004 article, "Long-Acting Injectable Risperidone" (2004;38:2122-7): Oral Risperidone was continued for the first 3 weeks of the study. Patients who received injections of 25, 50, or 75 mg received oral doses of 2, 4, and 6 mg, respectively.

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#### Correction: Role of low-molecular-weight heparin in invasive management of non-ST-elevation acute coronary syndromes

TO THE EDITOR: In this recent article (2004;38:2094-104), the enoxaparin bolus doses listed in Table 3 for both Ferguson trials (references 28 and 31) should be 0.3 mg/kg rather than 0.3 mg. Also, in the fourth sentence of the first paragraph under the Implications for Clinical Practice heading, the dose should be 0.3 mg/kg rather than 30 mg.

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Letters are subject to review prior to acceptance. They should address areas related to pharmacy practice, research, or education, or articles recently published. Corrections of previously published material also are accepted. Letters are limited to no more than five authors. In cases where adverse drug effects are described, the Naranjo ADR probability scale should be used to determine the likelihood that the adverse effect was drug-related (*Clin Pharmacol Ther* 1981;30:239-45). Text: limit 500 words. References: limit 5. Art: limit 1 table or figure.