

Letters to the Editor are welcomed. They may report new clinical or laboratory observations and new developments in medical care or may contain comments on recent contents of the Journal. They will be published, if found suitable, as space permits. Like other material submitted for publication, letters must be typewritten, double-spaced, and must not exceed **two** typewritten pages in length. No more than five references and one figure or table may be used. See "Information for Authors" for format of references, tables, and figures. Editing, possible abridgment, and acceptance remain the prerogative of the Editors.

Vitamin D Levels in Patients Seen in the Diabetes Unit of an Academic Medical Center

To the Editor: Although several studies have looked at vitamin D status in patients with diabetes, there is a paucity of data from practices specializing predominantly in diabetes. We assessed 25-hydroxyvitamin (OH) D levels in 133 patients (116 with type 2 and 17 with type 1 diabetes) seen in an outpatient diabetes unit of an academic medical center. Patients who had advanced congestive heart failure (New York Heart Association stage III and IV), active malignancy, stage 5 kidney disease, known vitamin D deficiency, or derangements of calcium-parathyroid metabolism were excluded. The group included 52 men and 81 women (89 Caucasian, 39 African American, and 5 Asian) with an average age of 54 years. Mean serum calcium was 9.45 mg/dL (reference range 8.6 to 10.2), average glycosylated hemoglobin (HbA1c) was 6.9%, mean serum creatinine was 1.06 mg/dL (reference range 0.5 to 1.3), and the majority (38/133, or 71.4%) had estimated glomerular filtration rate (eGFR) values greater than 60 mL/min. Following a recently proposed classification,¹ 68 patients (51.1%) were "deficient" (≤ 20

ng/mL), 32 patients (24%) were "relatively insufficient" (21–29 ng/mL), and only 33 patients (24.8%) qualified as having "sufficient" 25 (OH) vitamin D levels (≥ 30 ng/mL).

Our results show that the prevalence of vitamin D insufficiency in patients with diabetes seen in a specialty referral center is extremely high (75.2%). More than half of the subjects in our series were clearly deficient, whereas only one-fourth had levels considered optimal. Women, African Americans, younger patients, and those with poorer glycemic control had lower levels. Vitamin D status may be inversely related to insulin sensitivity,¹ but evidence regarding diabetes risk is unclear.^{2,3} Conversely, hyperglycemia may predispose to low vitamin D, or there may be associated factors common to both conditions (e.g. suboptimal nutritional status, older age, and lack of exposure to sunlight). Hypovitaminosis D may play a part in diabetic microvascular disease,⁴ and replacement may alleviate symptoms such as neuropathic pain.⁵ Studies exploring possible causes and correlates like degree of glycemic control, dietary intake, geographical factors, living conditions (e.g. housebound or institutional care), etc., are needed. Pending confirmatory data, consideration may be given to recommendations for screening for vitamin D deficiency in the diabetic population and evaluating the impact of different supplementation regimens on clinical outcomes.

Kanakasabai Narasimhan, MD, FACP

Ali A. Rizvi, MD, FACP, FACE

Division of Endocrinology, Diabetes and Metabolism
Department of Internal Medicine,
University of South Carolina School of Medicine,
Columbia, SC

References

1. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–281.
2. Hypponen E, Laara E, Reunanen A, et al. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001;358:1500–1503.
3. de Boer IH, Tinker LF, Connelly S, et al. Cal-

cium plus vitamin D supplementation and the risk of incident diabetes mellitus in the Women's Health Initiative. *Diabetes Care* 2008;31:701–707.

4. Suzuki A, Kotake M, Ono Y, et al. Hypovitaminosis D in type 2 diabetes mellitus: association with microvascular complications and type of treatment. *Endocr J* 2006;53:503–510.
5. Lee P, Chen R. Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. *Arch Intern Med* 2008;168:771–772.

Olanzapine-Induced Rabbit Syndrome

To the Editor: Rabbit syndrome (RS) is a distinct antipsychotic-induced extrapyramidal syndrome characterized by fine, rhythmic, and rapid movements of the perioral muscles along a vertical axis at a frequency of about 5 Hz, mimicking the chewing actions of a rabbit.¹ Although the exact prevalence of RS is unknown, it has been reported to occur in 4.4% of patients exposed to neuroleptics.²

A 35-year-old male with schizoaffective disorder presented with a nine month history of suspiciousness, excessive talking, irritability, and intermittent aggression. He had four previous schizoaffective episodes which had improved with typical antipsychotics without any adverse effects. He was treated with haloperidol up to 20 mg per day without improvement, but developed severe drug-induced Parkinsonism. Olanzapine 15 mg per day was started, along with trihexyphenidyl 4 mg per day, with improvement in his psychotic and Parkinsonian symptoms. But 15 days after starting olanzapine, he developed twitching movements of his upper lips, specifically on the right side, which was gradually replaced by rapid, rhythmic perioral movements involving both upper and lower lips in the vertical plane with a frequency of 4–5 Hz. These movements increased while doing motor tasks such as counting fingers. On the abnormal involuntary movement scale (AIMS), the abnormal lip movements were of moderate severity, and fine tremors of outstretched

hands and tongue were also noted. A diagnosis of olanzapine-induced rabbit syndrome was considered, and olanzapine was decreased to 12.5 mg per day. There was no worsening of psychopathology, but a gradual reduction in the frequency of perioral tremor occurrence was observed after 5 weeks and at the time of discharge from the hospital.

Rabbit syndrome has been reported to occur mostly with typical antipsychotics. Less frequently it is associated with atypical agents such as risperidone, olanzapine, aripiprazole, and clozapine.³ It has been seen as a late-appearing adverse effect, unlike our case which appeared after two weeks. There has been only one previous report in which olanzapine has been implicated as a cause of RS.⁴ Interestingly, olanzapine has helped in another patient with RS.⁵ The explanation that supersensitivity of dopamine receptors as the underlying mechanism of RS⁵ may be too simplistic, and the actual pathophysiology may vary between individuals. One possible strategy is dose reduction, which may be tried before switching antipsychotics or adding anticholinergic agents.

Samir Kumar Praharaj, MD, DPM
Sukanto Sarkar, MD, DPM
Amlan K. Jana, DPM
Vinod Kumar Sinha, MD, DPM
 Central Institute of Psychiatry
 Kanke, Ranchi
 Jharkhand, India

References

1. Villeneuve A. The rabbit syndrome. A peculiar extrapyramidal reaction. *Can Psychiatr Assoc J* 1972;17(suppl 2):S69.
2. Yassa R, Lal S. Prevalence of the rabbit syndrome. *Am J Psychiatry* 1986;143:656–657.
3. Catena Dell'osso M, Fagiolini A, Ducci F, et al. Newer antipsychotics and the rabbit syndrome. *Clin Pract Epidemiol Ment Health* 2007;3:6.
4. Sabolek M, Bayerle M. Rabbit syndrome due to olanzapine. *Psychiatr Prax* 2005;32:202–204.
5. Durst R, Katz G, Zislin J, et al. Rabbit syndrome treated with olanzapine. *Br J Psychiatry* 2000;176:193.

Further Indications for Capsule Endoscopy

To the Editor: In their excellent review from the April 2008 issue of the *Southern Medical Journal*, Sachdev and Ismail¹ briefly allude to the possibility of a role for capsule endoscopy in the follow up of celiac disease. In the latter context, capsule endoscopy has proven useful in the evaluation of patients with known celiac disease who have ongoing symptoms or alarm symptoms in spite of compliance with a gluten-free diet. In a prospective study of 47 such patients, the indications for capsule endoscopy included abdominal pain, cancer surveillance, blood in the stool, or persistent iron deficiency. At capsule endoscopy, ulceration was diagnosed in 21 patients, and there were isolated instances of adenocarcinoma, polyps, strictures, and intussusception. Nodularity was documented in six other patients and a submucosal mass in one other patient.² Consequently, for the purpose of diagnosing complications of celiac disease, capsule endoscopy has now been elevated to the status of a grade C recommendation.³ In view of the occasional association of celiac disease and inflammatory bowel disease,⁴ an additional indication might be the use of capsule endoscopy to establish or refute the coexistence of small bowel Crohn disease in patients with known celiac disease. The indications for capsule endoscopy enumerated by the authors¹ and others³ ought to apply not only to adults but arguably also to children, given the high prevalence of celiac disease and Crohn disease in the pediatric age group. In a study enrolling 87 children aged 18 months to 18 years, 77 were able to swallow the capsule. Nineteen of these were aged 7–10, and 58 were aged 11–18. Only 3 patients in the age group 7–18 were unable to swallow the capsule, but all 7 of their counterparts aged <7 failed to swallow the capsule. In that study, one of the principal advantages conferred by capsule endoscopy was to establish the real extent and severity of small

bowel involvement in 12 out of 22 patients with known Crohn disease. As a result, these patients had their medical treatment “increased or redesigned.”⁵ In 10 other patients, Crohn disease was suspected but not proven prior to capsule endoscopy. By identifying Crohn disease, capsule endoscopy enabled a definitive diagnosis in five of those patients.⁵

Oscar M. P. Jolobe, MRCP

Manchester Medical Society
 C/o John Rylands University Library
 Manchester, United Kingdom

References

1. Sachdev MS, Ismail MK. Capsule endoscopy: a review. *South Med J* 2008;101:407–414.
2. Culliford A, Daly J, Diamond B, et al. The value of wireless capsule endoscopy in patients with complicated celiac disease. *Gastrointest Endosc* 2005;62:55–61.
3. Sidhu R, Sanders DS, Morris AJ, et al. Guidelines on small bowel enteroscopy and capsule endoscopy in adults. *Gut* 2008;57:125–136.
4. Yang A, Chen Y, Scherl E, et al. Inflammatory bowel disease in patients with celiac disease. *Inflamm Bowel Dis* 2005;11:528–532.
5. de'angelis GL, Fornaroli F, de'Angelis N, et al. Wireless capsule endoscopy for pediatric small-bowel diseases. *Am J Gastroenterol* 2007;102:1749–1757; quiz 1748, 1758.

Hypersensitivity to Furosemide

To the Editor: “Drug eruptions are probably the most frequent of all manifestations of drug sensitivity.”¹ They range from mild, short-lived maculopapular rashes that subside, despite continuation of the medication, to severe forms such as Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN). In fact, “cutaneous drug eruptions occur in 2–3% of all hospitalized patients.”²

Furosemide has been found to produce cutaneous reactions in fewer than 5% of patients.³ These reactions can range from eczematous and psoriasis-like to bullous.⁴ In addition, furosemide—and other drugs with sulfhydryl moieties—have been found to produce other side effects in the pattern of a graft-versus-host disease.⁴

In our patient, the only side effect was the plaquous skin lesions which resulted in discomfort from itching and feelings of self consciousness related to her skin continuously desquamating (Fig 1). Her self consciousness added to depression about being ill and led to a self-induced social isolation. Since she was admitted to rehab with a diagnosis of psoriasis and multiple allergies (though not to furosemide or sulfonamides), it was presumed that she had severe psoriasis. She was treated with pimecrolimus, coal tar shampoo, and ammonium lactate, with minimal transient relief. It was therefore presumed that her psoriasis was resistant to standard treatment.

A dermatologist described her skin as generalized, disseminated, symmetric, and plaquous. After a review of her extensive list of allergies, it was determined—although no antibiotics were among her hypersensitivities—that the patient was likely

hypersensitive to furosemide. The recommendation was made to discontinue furosemide and start bumetanide. Upon looking for any previous reports of substituting bumetanide for furosemide—even though bumetanide was also a sulfonamide loop diuretic, like furosemide—there were only two previously documented cases, in which there was no cross-allergy between the two drugs.^{5,6} In one of those cases, after 29 days, the patient was accidentally put on furosemide again; at which point his skin had a cutaneous eruption within three hours of exposure to the drug. As soon as he was put back on bumetanide, his skin again cleared up.⁶

Upon one day without furosemide, our patient's skin quit itching and was less erythematous (Fig 2). There was also a decrease in desquamation overnight. She felt much better about herself and was much happier to be around people as well.



Fig. 1 The patient's palm showing desquamation while taking furosemide.



Fig. 2 The patient's palm one day after replacing furosemide with bumetanide.

Acknowledgment

We would like to thank Kevin M. Means, MD, for his assistance.

Catherine I. Dalton, MD

Marilyn S. Pacheco, MD

Department of Physical Medicine and Rehabilitation
University of Arkansas for Medical Sciences
Little Rock, AR

References

1. Breathnach SM. Adverse cutaneous reactions to drugs. *Clin Med* 2002;2:15–19.
2. Brönnimann M, Yawalkar N. Histopathology of drug-induced exanthems: is there a role in diagnosis of drug allergy? *Curr Opin Allergy Clin Immunol* 2005;5:317–321.
3. Noce R, Paredes BE, Pichler WJ, et al. Acute generalized exanthematic pustulosis (AGEP) in a patient treated with furosemide. *Am J Med Sci* 2000;320:331–333.
4. Kitamura K, Aihara M, Osawa J, et al. Sulfhydryl drug-induced eruption: a clinical and histological study. *J Dermatol* 1990;17:44–51.
5. Bourgain C, Bienvenu T, Cremieux AC, et al. Bumetanide as replacement therapy in furosemide-induced vasculitis. *Presse Méd* 1990;19:1504–1505 (in French).
6. Gratadour P, Guillaume C, Bui-Xuan B, et al. Absence of cross-allergy between furosemide and bumetanide. *Presse Méd* 1990;19:1504 (in French).

Could Sertraline Afford Protection Against Atherosclerosis? A Medical Hypothesis

To the Editor: The local oxidation of low density lipoprotein (LDL) within atherosclerotic lesions is widely believed to be of importance in the pathogenesis of atherosclerosis.¹ The oxidized LDL promotes adhesion of monocytes to endothelial cells,² causes an increase in the production of metalloproteinase that would probably destabilize the fibrous caps over advanced lesions,³ and induces apoptosis in cells.⁴ Macrophages transform into foam cells by incorporating oxidized LDL using several kinds of scavenger receptors.⁵

Recently, Wen and Leake⁶ showed that LDL oxidation occurs not within the interstitial fluid of atherosclerotic

lesions but within lysosomes in macrophages in atherosclerotic lesions. The initial oxidation in the lysosomes may be of aggregated LDL, but the oxidation may continue as the LDL particles are degraded by the lysosomal lipases and proteases. The release of oxidized lipids from the lysosomes into the rest of the cell, the engorgement of the lysosomes partly attributable to ceroid, or the inactivation of lysosomal enzymes by oxidized LDL⁷ may possibly lead to the alteration of cell function in an atherogenic manner.

Increasing the pH of lysosomes may inhibit the oxidation of LDL within these organelles, as LDL oxidation can be promoted by acidic pH.⁸ Weak bases in their nonionized state permeate membranes and accumulate in the acidic interior of lysosomes where they are protonated and thus become unable to diffuse back into the cytosol. In such a way, they increase the pH of lysosomes and can interfere with the process of oxidation of LDL in the lysosomes.⁹

In previous studies it has been demonstrated that among the antidepressants, sertraline shows the highest degree of accumulating and increasing the pH of the acidic interior of lysosomes.¹⁰ Given this strong lysosomotropic property, it can be hypothesized that sertraline may inhibit LDL oxidation within lysosomes in macrophages in atherosclerotic lesions and therefore reduce the risk of atherosclerosis. Further studies are needed to survey this antiatherosclerotic effect.

Arash Mowla, MD

Department of Psychiatry
The Persian Gulf Biomedical Sciences
Research Institute
Bushehr University of Medical Sciences
Bushehr, Iran

M. R. Namazi, MD

Department of Dermatology
Shiraz University of Medical Sciences
Shiraz, Iran

References

1. Chisolm GM, Steinberg D. The oxidative modification hypothesis of atherogenesis: an overview. *Free Radic Biol Med* 2000;28:1815–1826.

2. Navab M, Berliner JA, Watson AD, et al. The Yin and Yang of oxidation in the development of the fatty streak—a review based on the 1994 George Lyman Duff Memorial Lecture. *Arterioscler Thromb Vasc Biol* 1996;16:831–842.
3. Rajavashisth TB, Liao JK, Galis ZS, et al. Inflammatory cytokines and oxidized low density lipoproteins increase endothelial cell expression of membrane type 1-matrix metalloproteinase. *J Biol Chem* 1999;274:11924–11929.
4. Reid VC, Hardwick SJ, Mitchinson MJ. Fragmentation of DNA in P388D₁ macrophages exposed to oxidized low-density lipoprotein. *FEBS Lett* 1993;332:218–220.
5. Steinberg D, Witztum JL. Is the oxidative modification hypothesis relevant to human atherosclerosis? Do the antioxidant trials conducted to date refute the hypothesis. *Circulation* 2002;105:2107–2111.
6. Wen Y, Leake DS. Low density lipoprotein undergoes oxidation within lysosomes in cells. *Circ Res* 2007;100:1337–1343.
7. O'Neil J, Hoppe G, Sayre LM, et al. Inactivation of cathepsin B by oxidized LDL involves complex formation induced by binding of putative reactive sites exposed at low pH to thiols on the enzyme. *Free Radic Biol Med* 1997;23:215–225.
8. Morgan J, Leake DS. Oxidation of low density lipoprotein by iron or copper at acidic pH. *J Lipid Res* 1995;36:2504–2512.
9. Ohkuma S, Poole B. Fluorescence probe measurement of intralysosomal pH in living cells and perturbation of pH by various agents. *Proc Natl Acad Sci USA* 1978;75:3327–3331.
10. Daniel WA, Wójcikowski J, Pałucha A. Intracellular distribution of psychotropic drugs in the grey and white matter of the brain: the role of lysosomal trapping. *Br J Pharmacol* 2001;134:807–814.

Perforated Stercoral Ulcer of the Sigmoid Colon

To the Editor: Stercoral ulcer formation and perforation of the colon is a rare condition affecting patients with severe chronic constipation. There may be an underestimation of the incidence, since many stercoral ulcer-related colon perforations may be incorrectly identified as spontaneous, idiopathic, or secondary colonic perforations related to diverticulitis, ischemia, etc. We present here two cases and a brief review of the literature.

In the first case, an 84-year-old female presented after experiencing ab-

dominal pain for 2 to 3 days and severe constipation for 2 to 3 months. On examination she was hemodynamically stable and in no acute distress. Her abdominal examination did not reveal peritoneal signs. Within 24 hours she deteriorated, with increasing abdominal pain and respiratory distress. Overnight she developed peritoneal signs and hypotension. Urgent surgical exploration revealed fecal peritonitis secondary to sigmoid perforation. A large amount of scybala was seen in the pelvis and inside the colon. A perforation site was seen at the antimesenteric side of the sigmoid colon. A sigmoid colectomy with colostomy was performed. Pathology showed transmural inflammation consistent with perforation and no malignancy.

In the second case, a 41-year-old female presented with new onset abdominal pain for 2 days. She had experienced constipation for 1 to 2 months. The patient was in considerable discomfort. She was tachycardic, and had peritoneal signs. She was taken to the operating room where she underwent abdominal exploration. Fecal peritonitis was encountered. Several hard stools were seen in the pelvis as well as inside the colon. A perforation site was seen at the antimesenteric side of the sigmoid colon. Pathology showed transmural acute inflammation, consistent with perforation. No malignancy was identified.

Both cases revealed a sigmoid perforation meeting criteria set in the literature.¹ Both patients presented with abdominal pain rapidly evolving to peritonitis. Both patients had longstanding constipation, and the large bowel contained rock-hard fecal material. No primary obstructive, inflammatory or vascular disease of the colon was identified. Both patients were treated with a Hartmann staged procedure. Perforations appeared as single lesions that seemed to have been punched out. Both perforations were located at the antimesenteric border of the bowel wall. Both specimens showed transmural necrosis.

Severe chronic constipation is considered the main causative factor in the

development of stercoral ulcer formation and perforation of the colon. Chronic constipation leads to the formation of rock-hard feces that may be present for months and may calcify (scybal). They exert a constant pressure on the bowel wall and lead to pressure necrosis of the mucosa and subsequently the entire bowel wall.¹ The most commonly affected site is the antimesenteric side of the colonic wall, where the blood supply of the bowel wall is the lowest and is highly dependent on capillary perfusion. The increased intraluminal pressure may exceed the capillary perfusion pressure and lead to focal ischemia. The sigmoid is particularly involved.¹⁻³

Abdominal x-rays show marked fecal loading in most instances. Calcified feces (scybal) are rare (up to 20%) but are a strong index of stercoral ulcer. Free air will be present in the majority of patients with perforated colon. The combination of free air and a history of substantial constipation should raise the suspicion of stercoral ulcer perforation.

In terms of managing the perforated stercoral ulcer, resection of the involved segment and exteriorization of the colon is probably the best option to avoid anastomotic leakage. Other therapeutic approaches such as primary repair of the ulcer or simple exteriorization of the colon without resection have been previously refuted in the literature.¹⁻³ Controversy still surrounds the best way to manage the stercoral ulcer that has not yet perforated in patients with chronic severe constipation, abdominal pain, and radiographic evidence of scybal. These patients should probably be managed conservatively with a high fiber diet, stool softeners, laxatives, plenty of hydration, and enemas.

Ioannis S. Hatzaras, MD

Department of Surgery
Ohio State University
College of Medicine
Columbus, OH

Scott Armen, MD

Department of Surgery
Ohio State University

College of Medicine
Columbus, OH
Stanley J. Dudrick, MD

Department of Surgery
Saint Mary's Hospital
Yale University School of Medicine
Waterbury, CT

References

1. Maurer CA, Renzulli P, Mazzucchelli L, et al. Use of accurate diagnostic criteria may increase incidence of stercoral perforation of the colon. *Dis Colon Rectum* 2000;43:991-998.
2. Serpell JW, Nicholls RJ. Stercoral perforation of the colon. *Br J Surg* 1990;77:1325-1329.
3. Guyton DP, Evans D, Schreiber H. Stercoral perforation of the colon. Concepts of operative management. *Am Surg* 1985;51:520-522.

Cyanoacrylate-Related Pulmonary Embolism Following Percutaneous Varicocele Embolization

To the Editor: As an effective means of varicocele treatment, percutaneous embolization has been shown to be equal to surgical spermatic vein ligation. It is also associated with less postprocedure discomfort. Cyanoacrylates are the main liquid adhesives used in endovascular procedures and have an important role in managing vascular abnormalities.¹

We report a case of a symptomatic pulmonary embolus of enbucrilat, an

n-butyl cyanoacrylate, (Histoacryl[®], Braun, Tuttlingen, Germany) after percutaneous embolization of a varicocele: a 36-year-old male with a history of recurrent varicocele underwent percutaneous embolization of the left spermatic vein. After right femoral vein catheterization, a coaxial catheter was passed via the left renal vein and left internal spermatic vein to the level of the inguinal ligament. A mix of 0.5 mL of enbucrilat and 2.5 mL of ethiodized oil (Lipiodol[®] Ultra-Fluide, Guerbet, France), was injected. The patient almost immediately experienced a dry cough, sinus tachycardia, chest discomfort, tachypnea, and mild dyspnea. These symptoms persisted for a few hours. On immediate chest x-ray, multiple small opacities were seen in both lung fields (Fig.). Echocardiography showed mild elevation of right ventricular systolic pressure (RVSP) at 34 mm Hg. Treatment was conservative; the patient was discharged after 3 days. Three months later he was asymptomatic; his RVSP was normal.

Because of their low viscosity, cyanoacrylates are easy to deliver through microcatheters. Their lack of radio-opacity and their rapid polymerization when in contact with blood can make precise, safe occlusion difficult to achieve. Modifications to address these problems in-



Fig. Chest x-ray. Multiple small opacities in both lungs (white arrows).

clude the addition of powdered metals and iodized oils. Iodized oils not only opacify the agent, but also slow the polymerization time. The lungs typically filter most emboli; systemic embolization is possible through an arteriovenous malformation in the lungs or through an atrial septal defect.²

Glue embolism should be suspected when cough, tachycardia, pleuritic chest pain, dyspnea or hypoxia occur after percutaneous embolization with cyanoacrylate. Chest radiography or noncontrast-enhanced computed tomography will substantiate the diagnosis of glue-related pulmonary emboli. Emboli are seen as scattered radio-opaque material in the lung fields. These are likely to be missed on computed tomographic pulmonary angiography, if the bone windows are not reviewed carefully. It is important to differentiate glue emboli from conventional thromboemboli, as glue emboli require only symptomatic care.³

The deposition of cyanoacrylate within a vessel results in an acute inflammatory reaction in the wall and surrounding tissues. This progresses to a chronic and granulomatous process with foreign body giant cells and fibrosis. Although the occlusion created by the glue may be permanent, recanalization has also been observed.²

Information about cyanoacrylates is especially important because of the recent approval of n-butyl cyanoacrylate by the United States Food and Drug Administration.² As cyanoacrylate vascular procedures are performed more frequently, glue embolization will become more common. A high index of suspicion and the proper selection and interpretation of diagnostic imaging are necessary to make this diagnosis.

Likargos Kolilekas, MD
Ioannis Kalomenidis, MD
Effrosyni Manali, MD
Christina Triantafyllidou, MD

2nd Pulmonary Department
National and Kapodistrian University of Athens

“Attikon” University Hospital,
Athens, Greece

Elias Brountzos, MD

2nd Radiology Department,
National and Kapodistrian University of Athens

“Attikon” University Hospital,
Athens, Greece

Spyros Papiris, MD, FCCP, PhD

2nd Pulmonary Department,
National and Kapodistrian University of Athens,

“Attikon” University Hospital
Athens, Greece

References

1. Shlansky-Goldberg RD, VanArsdalen KN, Rutter CM, et al. Percutaneous varicocele embolization versus surgical ligation for the treatment of infertility: changes in seminal parameters and pregnancy outcomes. *J Vasc Interv Radiol* 1997;8:759–767.
2. Pollak JS, White RI Jr. The use of cyanoacrylate adhesives in peripheral embolization. *J Vasc Interv Radiol* 2001;12:907–913.
3. Rickman OB, Utz JP, Aughenbaugh GL, et al. Pulmonary embolization of 2-octyl cyanoacrylate after endoscopic injection therapy for gastric variceal bleeding. *Mayo Clin Proc* 2004;79:1455–1458.

Carisoprodol Should be Taken Off the Market

To the Editor: In an editorial in the February edition of the *Southern Medical Journal*, Reeves and Burke¹ advocate that carisoprodol (Soma[®] Meda Pharmaceuticals, Inc; Somerset, NJ) should become a controlled substance. During the last few years, three other papers have been published by American researchers addressing the possible abuse of this centrally acting muscle relaxant.^{2–4} The research paper accurately points to the abuse potential of carisoprodol⁴ and the increasing extent of this problem,^{2,3} arguing that carisoprodol should be a controlled substance.^{1,2} We follow this research and debate with interest. For several years and on several occasions these researchers, along with other US data, have provided us with valuable information in our own research into this field. We would therefore like to offer a comment on these valuable publications.

We have recently published a pharmacoepidemiological paper from Norway that addresses the problem of carisoprodol abuse in a broader and unbiased manner.⁵ The paper demonstrates, by the use of a complete and national prescription database, that the abuse of carisoprodol is not a marginal or rare problem confined to the occasional case report or case series but, rather, a phenomenon that affects many users of the drug. As Reeves and Burke¹ report in their editorial, there might also be additional illegal imports that will be unregistered—even in national prescription databases.

The abuse of carisoprodol is but one of the problems with this drug. A major topic may be the narrow therapeutic index of the drug with high reports on toxicity.^{6,7} Furthermore, because carisoprodol holds the potential for traffic-related impairment,⁸ users of carisoprodol have an increased risk of being involved in traffic accidents.⁹ On the basis of these three problematic aspects of carisoprodol and the perceived marginal therapeutic advantages of the drug, the Norwegian Medicines Agency has gone even further than the suggestions of Reeves and Burke and revoked the market authorization for carisoprodol in Norway (effective May 1, 2008).¹⁰ The European Medicines Agency has supported this and issued a recommendation for the withdrawal of the drug from all European Union member states. The interested reader can find a comprehensive review of the literature and the process of taking the drug off the European market in a newly published article in the *Norwegian Journal of Epidemiology*.¹¹ An understanding of how this process has proceeded in Europe might help US authorities in their efforts concerning this problematic drug.

Jørgen G. Bramness, MD, PhD
Svetlana Skurtveit, MSc, PhD

Division of Pharmacoepidemiology
Norwegian Institute of Public Health
Oslo, Norway

References

1. Reeves RR, Burke RS. Is it time for carisoprodol to become a controlled substance at the federal level? *South Med J* 2008; 101:127–128.
2. Reeves RR, Hammer JS, Pendarvis RO. Is the frequency of carisoprodol withdrawal syndrome increasing? *Pharmacotherapy* 2007;27:1462–1466.
3. Forrester MB. Carisoprodol abuse in Texas, 1998–2003. *J Med Toxicol* 2006;2:8–13.
4. Owens C, Pugmire B, Salness T, et al. Abuse potential of carisoprodol: a retrospective review of Idaho Medicaid pharmacy and medical claims data. *Clin Ther* 2007;29:2222–2225.
5. Bramness JG, Furu K, Engeland A, et al. Carisoprodol use and abuse in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol* 2007;64:210–218.
6. Høiseith G, Bramness JG, Christophersen AS, et al. Carisoprodol intoxications: a retrospective study of forensic autopsy material from 1992–2003. *Int J Legal Med* 2007;121:403–409.
7. Høiseith G, Sørlid H, Bramness J. Carisoprodol intoxications: contacts to the Norwegian Poisons information 1999–2004. *Clin Toxicol (Phila)* 2007;46:307–309.
8. Logan BK, Case GA, Gordon AM. Carisoprodol, meprobamate, and driving impairment. *J Forensic Sci* 2000;45:619–623.
9. Bramness JG, Skurtveit S, Mørland J, et al. The risk of traffic accidents after prescriptions of carisoprodol. *Accid Anal Prev* 2007; 39:1050–1055.
10. Buajordet I, Madsen S. [Somadril recalled in Norway]. *Tidsskr Nor Laegeforen* 2007;127: 1397.
11. Bramness J, Buajordet I, Skurtveit S. The role of pharmacoepidemiological studies in the market withdrawal of carisoprodol (Somadril®) in Europe. *Nor J Epidemiol* 2008;18:167–172.

*I am the ghost of Shadwell Stair,
 Along the wharves by the water-house,
 And through the cavernous slaughter-house,
 I am the shadow that walks there.
 Yet I have flesh both firm and cool,
 And eyes tumultuous as the gems
 Of moons and lamps in the full Thames
 When dusk sails wavering down the pool.
 Shuddering the purple street-arc burns
 Where I watch always; from the banks
 Dolorously the shipping clanks
 And after me a strange tide turns.
 I walk till the stars of London wane
 And dawn creeps up the Shadwell Stair.
 But when the crowing syrens blare
 I with another ghost am lain.*

—Wilfred Owen
 Shadwell Stair