Tolerability of Rofecoxib versus Naproxen

TO THE EDITOR: The article comparing rofecoxib with naproxen (1) appears to have been mistakenly published in the editorial pages of *Annals* rather than the advertising section, where it seems to belong. The article was supported by Merck & Co. and written by employees or consultants of Merck. In addition, requests for reprints go to Merck. All of this might be reasonable if the article included any new, fair, or reasonable information.

Selective cyclooxygenase-2 inhibitors (coxibs) as a subset of nonsteroidal anti-inflammatory drugs (NSAIDs) have been available for more than 5 years and are generally accepted as having less gastrointestinal (GI) toxicity than older NSAIDs, to some degree. This marginal advantage comes at considerable extra cost in most patients without extra risk factors, and a recent *Annals* article concluded that coxibs were not cost-effective (2).

In evaluating “tolerability,” it would be fair to select reasonable doses of medications being evaluated. The authors selected naproxen, 500 mg twice daily, in a sample with a mean age of 63 years. Naproxen was introduced in 1974 as a 250-mg tablet to be given twice daily. A few years later, a 375-mg tablet was approved, and it was 4 to 8 more years before the 500-mg tablet became available. A starting dosage of 500 mg twice daily appears unjustified in elderly patients with osteoarthritis, since increasing NSAID doses usually result in greater increases in GI intolerance than in effectiveness; in addition, the 50-mg maximum rofecoxib dose was not used in the study.

Lisse and colleagues’ article seems to me to contribute nothing new or useful to osteoarthritis care. It will mainly serve as a handout for Merck reps to “prove” that rofecoxib is the drug of choice for all patients with osteoarthritis.

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References

TO THE EDITOR: In the article by Lisse and colleagues (1), the real message of a head-to-head comparison of rofecoxib and naproxen was obscured. Regarding discontinuation of treatment due to clinical adverse events, Figure 1 shows that 374 of 2785 patients receiving rofecoxib stopped treatment. In the naproxen group, 386 of 2788 patients had clinical adverse events and cessation of therapy. On my calculator, these data show that the rate of discontinuation due to adverse events was 13.4% in the rofecoxib group and 13.9% in the naproxen group.

While the rate of GI intolerance may be lower with rofecoxib, to me the drugs seem equally effective and equally well tolerated. The major difference most of us in practice (and our patients) see is the cost. I find it distasteful to play up mildly different rates of GI symptoms and ignore the virtually identical rates of overall clinical complications.

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Reference

TO THE EDITOR: If Lisse and colleagues (1) reported a completely new data set, it would be possible to perform a meta-analysis of their data set and that of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study (2). On an intention-to-treat basis, Lisse and colleagues showed that rofecoxib does not statistically differ from naproxen in rates of withdrawal for clinical and laboratory adverse events combined. Therefore, to make up for rofecoxib’s better GI tolerability, other adverse events must have occurred. One was myocardial infarction.

In the intention-to-treat analysis, 5 of 2799 patients in the rofecoxib group and 1 of 2787 patients in the naproxen group had myocardial infarctions. If we combine these statistics with data from Konstam and colleagues’ study (3), in which 37 fatal and nonfatal cardiac events occurred among 9083 patients taking rofecoxib versus 10 fatal and nonfatal cardiac events among 7870 patients taking naproxen, we would find that an overview of the published trials of rofecoxib versus naproxen yields a relative risk for cardiac events of 3.4 (95% CI, 1.7 to 6.5) with rofecoxib.

Such amalgamation is made more transparent and accurate if authors use the same criteria as a quoted reference to classify side effects. Given the suspected ability of NSAIDs such as ibuprofen to block the cardioprotective antiplatelet actions of aspirin (4), the cardiovascular issues in a trial in which patients were allowed to take both aspirin and the trial NSAIDs promised to be interesting. Lisse and colleagues did not provide sufficient data to exclude the possibility that rofecoxib acted as a partial antagonist to aspirin or otherwise promoted the events that lead to myocardial infarction.

In conclusion, the relative cardiac safety of rofecoxib remains open to question, and the data trends are not reassuring.

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References
IN RESPONSE: It is important to understand differences between dual cyclooxygenase-inhibiting NSAIDs and coxibs for effective use in appropriate populations. The ADVANTAGE (Assessment of Differences between Vioxx And Naproxen To Ascertain Gastrointestinal tolerability and Effectiveness) study was the largest trial to enroll patients with osteoarthritis using less restrictive entry criteria. In addition, it permitted use of low-dose aspirin during the trial and involved a sample that was characteristic of patients seen in clinical practice with typical comorbid conditions. Treatment of osteoarthritis with rofecoxib and naproxen in this setting was designed to study “real-world” conditions. Other important coxib studies, such as the VIGOR study, which included patients with rheumatoid arthritis who were not taking low-dose aspirin, and CLASS (Celecoxib Long-term Arthritis Safety Study), which included both patients with osteoarthritis and those with rheumatoid arthritis and permitted low-dose aspirin, had differences in design (1, 2).

Our study design compared the highest doses of rofecoxib and naproxen indicated for long-term use in patients with osteoarthritis, according to prescribing information, to fully assess potential differences in tolerability. As pointed out by Dr. Hanauer, a higher dose of rofecoxib, 50 mg, is available; however, it is not recommended for long-term use. The main benefit of coxibs compared with NSAIDs relates to GI side effects, a major cause of drug-induced morbidity and mortality. Our study and VIGOR (1) demonstrated improved general GI tolerability and reductions in serious GI events (perforations, ulcers, GI bleeding) with rofecoxib compared with naproxen. As noted by Drs. Ruschen and Jenkinc, discontinuation due to causes other than GI events, which were not prespecified or powered for in our study, may be similar with these medications. The meta-analysis by Konstam and colleagues emphasizes one issue briefly mentioned by Dr. Emanuel in his perspective on the lessons of SARS (1), namely the stress on hospital facilities and health care workers. Managing SARS was an incredibly labor-intensive effort, making tremendous demands on everyone involved. Properly donning the personal protective equipment took 10 to 20 minutes, and the reverse process was equally time-consuming. In one isolation hospital dedicated to SARS, personnel were on the ward from 8:00 a.m. to 5:00 p.m., always dressed in 1 or 2 layers of protective equipment, adding another layer to enter individual patient rooms. The staff were not allowed to eat or drink the entire 9 hours they were on the ward. In our institution, the patients potentially most in need of immediate care, especially those with impending respiratory failure or those who were already on ventilators, were the ones who posed a significant danger to staff because of increased secretions and possible aerosolization of the virus.

We were perhaps fortunate in Taiwan that our outbreak came somewhat later than elsewhere, so that we benefited from the experience of others. But that did not eliminate the anxiety. The haggard faces and slumping shoulders of our staff early in the epidemic told us that we were doing the right things, and faces began to brighten. However, we realized we were doing the right things, and faces began to brighten. Should another outbreak of SARS occur, we believe the protective measures are effective, but it would still be terrifically burdensome. I have the highest respect for our personnel who were on the front lines.

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References
lines last spring. With them, I heartily pray we don’t have to repeat the experience.

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Reference

Improving Geriatrics Training

TO THE EDITOR: “Every internist a geriatrician,” the prevailing sentiment behind the Annals supplement on improving geriatrics training (1), is a statement of hope for the future but does not reflect current reality. Taking care of old people does not qualify an internist as a geriatrician, just as taking care of patients with arthritis does not qualify one as a rheumatologist. Just as there will never be (nor should there be) enough rheumatologists to care for all of the patients with arthritis, the fact that there will never be enough geriatricians to care for all the frail elders is irrelevant.

That “internists and family physicians play an important role in the care of older people” (2) is indisputable. Likewise, few would dispute that current trainees lack the knowledge base and ability to adequately care for frail elders when they enter practice. Furthermore, the Annals supplement (1) demonstrates that most trainees are not particularly interested in the knowledge base needed to care for frail elders, perhaps because it is so difficult to apply it effectively in the community within our current practice structures and financing.

Geriatric medicine exists to push the agenda forward, to be at the forefront of reforming the process and financing of care for the benefit of our aging nation. Dr. Hazzard (3) asks the rhetorical question, “Where do geriatricians fit in this world?” I believe his answer, “principally in academic health centers,” reflects a major intellectual stumbling block in the growth, indeed perhaps in the survival, of the field of geriatric medicine.

There is a tremendous market demand for geriatricians and geriatric skills in the community. The services offered by geriatricians that are most often lacking in a general medicine or family medicine practice include staff sensitivity to the needs of functionally impaired elders; longer time allotments for office visits, more in-depth analysis of cognitive, affective, and functional status; willingness to assess decision-making capacity; analysis of geriatric syndromes (falls, delirium, dementia, incontinence, polypharmacy); greater willingness to discuss goals of care, advance care planning, and advance directives with patients and families; greater knowledge of community resources; ability to see patients and function effectively in various sites of care, such as nursing homes, assisted living facilities, or patients’ homes; ability to help coordinate transitions across sites of care; enhanced skills in end-of-life care; ability to function as a member of a treatment team; and use of office mechanisms for efficient processing of associated paperwork and case–care management.

Community-based geriatric medicine serves as a classic example of market failure. Despite the demand, adequate reimbursement of such service is lacking. A typical geriatric medicine practice must rely on Medicare for 90% of its reimbursement. In 2002, when the Medicare physician reimbursement rates were decreased by 5.5%, costs increased by 10% (4).

The only way for geriatric medicine to survive (whether it is practiced by fellowship-trained geriatricians or geriatrically trained and oriented internists or family physicians) and for the needs of frail elders to be met is for the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration) to address the market failure that it has caused. If the practice of geriatric medicine is made financially viable in the community, if the job opportunities appear, the interest of the trainees will follow.

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References

Hospital Procedure Volume and Outcomes

TO THE EDITOR: The article by Meyerhardt and colleagues (1) examined the effect of hospital volume on outcomes in patients with colon cancer following resection surgery. The use of clinical trial data rather than administrative claims data strengthened the study because it allowed the researchers to adjust for additional covariates, such as the number of positive lymph nodes, as well as model for recurrences recorded prospectively. The researchers did an excellent job of validating the Medicare procedure volume by comparing it with the Nationwide Inpatient Sample database. The researchers adjusted for any potential “clustering” that may have arisen because of high correlation between outcomes of patients treated by the same surgeon, as referenced in the study by Panageas and colleagues (2), by using a robust sandwich estimator to adjust standard errors for clustering of cases within hospitals.

However, statistically adjusting for clustering still does not compensate for the lack of information or data regarding potential predictors of outcomes in this study. From a conceptual point of view, we feel that certain surgeon-specific factors such as American Board of Surgery certification and years of experience since year of certification, which are valid predictors of death, should have been included in the models (3). Also, certain hospital-specific factors such as the nature of ownership (for-profit vs. not-for-profit) and geographic location (rural vs. urban) should have been included (4). All of the above-mentioned factors have been shown to predict outcomes after resection surgery in patients with colon cancer (3, 4). Even if the data did not permit including these factors as covariates,
Letters

this should have been mentioned as a potential limitation in the Discussion section.

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References

IN RESPONSE: Mr. Joshi and Dr. Miller note that both surgeon- and hospital-specific factors may be important predictors of outcome. The articles by Prystowsky and colleagues (1) and Ko and associates (2) examined the impact of such factors on short-term outcomes, particularly in hospital morbidity and mortality and length of stay. We were particularly interested in looking beyond short-term end points and examining whether the hospital where a colon cancer resection is performed predicts long-term mortality and cancer recurrences. Of interest, the number of surgeries was associated with over-resection is performed predicts long-term mortality and cancer recurrences. We did not have information on individual surgeons, although recent reports have demonstrated conflicting relative importance between hospital and surgeon volumes (3, 4). Furthermore, the recent movements toward regionalization and procedure volume thresholds have focused on hospital procedure volumes, thereby underscoring the need to further understand what such volumes truly mean.

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References

Clinical Observation

Editor’s Note: The lead author of the following Clinical Observation was one of a dozen Associates of the American College of Physicians selected to present a clinical vignette at the 2002 Annual Session in Philadelphia. We are proud to present this case report through a special arrangement with the Council of Associates of the College.

Isolated Gastric Varices Occurring 5 Years after Chemotherapy for Splenic Lymphoma

TO THE EDITOR: Background: Isolated gastric varices result from sinistral (left-sided) portal hypertension due to splenic vein obstruction (1, 2). Known causes of splenic vein obstruction are pancreatitis (65%); pancreatic neoplasm (18%); and Weber–Christian disease, hepatic cirrhosis, umbilical vein catheterization, renal-cell carcinoma, abdominal surgery, and trauma (17% cumulative) (2). This report describes a patient who developed isolated gastric varices due to splenic vein obstruction 5 years after chemotherapy for splenic lymphoma.

Case Report: A 73-year-old man presented with melena. He reported no use of nonsteroidal anti-inflammatory medications and glucocorticoids and had no other gastrointestinal symptoms. Five years earlier, he had been treated for non-Hodgkin follicular center, large-cell lymphoma confined to the spleen. Complete remission was achieved with 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. The patient did not receive radiation therapy. His supine blood pressure and pulse were 100/60 mm Hg and 110 beats/min, respectively. On standing, his blood pressure dropped to 86/48 mm Hg and his heart rate increased to 122 beats/min. Results of the remainder of the physical examination were normal. His blood hemoglobin level and hematocrit were 63 g/L and 0.19, respectively. Platelet count, international normalized ratio, and activated partial thromboplastin time were normal, as were levels of serum amylase and lipase, hepatic aminotransferases, alkaline phosphatase, and serum bilirubin.

Transfusion of 4 units of whole blood raised the patient’s blood pressure to 116/70 mm Hg and his hemoglobin level to 98 g/L. Upper endoscopy showed massive varices involving the gastric cardia and fundus, but not the esophagus. A computed tomogram of the abdomen was normal. Splenic angiography showed a normal splenic artery. A 1.5-cm segmental occlusion of the splenic vein within and contiguous to the splenic hilum was present during the venous phase (Figure). Retrograde flow in splenic venous tributaries fed large gastric varices through collateral vessels (Figure). The gastric varices gave rise to collateral vessels that supplied and reconstituted the splenic vein distal to the obstruction (Figure). The remaining portions of the splenic vein, the portal vein, and intrahepatic portal tributaries were patent. Results of celiac arteriography and hepatic venography with hemodynamic measurements were normal. Protein C and S activity, antithrombin III activity, and plasma homocysteine concentration were normal. Antinuclear antibodies, antithromboplastin
Spleen (S) consists of a darker central region (hilum) and lighter peripheral region (pulp). The splenic vein (black arrow) is reconstituted by collateral vessels from isolated gastric varices (white arrow). No direct venous conduit is noted from the splenic hilum to the reconstituted splenic vein because of intra- and peri-hilar splenic vein obstruction. Splenic hilum is darker than splenic pulp because increased venous congestion and collateral vessels supply short gastric veins and ultimately isolated gastric varices. The distal splenic vein drains into the portal vein near the liver (L) hilum.

Splenectomy was performed. Gross and histologic findings included dilated, tortuous, and nodular vessels in the hilum consisting of hyalinized sclerotic veins with no lumina. Thrombus was present in contiguous venous tributaries. There was no arterial thrombosis. Fibrocongestive splenomegaly was present, and there was no residual lymphoma.

Discussion: Sinistral portal hypertension is characterized by isolated gastric varices, splenomegaly, and normal hepatic function (1). It results from splenic vein obstruction (1, 2), which causes pressure to rise in splenic venous tributaries, producing retrograde flow into collaterals that supply the short gastric veins (1–4). This causes dilatation of submucosal veins in the gastric cardia and fundus, which give rise to gastric varices (1–4). Bridging collaterals from these varices may reconstitute the splenic vein distal to the obstruction or may drain into the portal vein itself (1–4). The cause of splenic vein obstruction in this case is uncertain. We speculate that it relates to inflammation from tumor lysis during chemotherapy.

Splenectomy is the most effective procedure for treating isolated gastric varices (1, 3). Splenic artery embolization has produced less satisfactory results (4). More recently, endoscopic gastric sclerotherapy has been used effectively for acute treatment of isolated gastric varices, but its long-term efficacy is unknown (5).

Conclusion: In our patient, isolated gastric varices due to intrasplenic occlusion of the splenic vein occurred 5 years after chemotherapy for splenic lymphoma. Patients with this complication may require splenectomy if upper gastrointestinal hemorrhage from isolated gastric varices ensues.

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References

CORRECTION

Correction: Hospital Procedure Volume and Outcomes

In an article on association of hospital procedure volume and outcomes in patients with colon cancer (1), Table 1 contained an error. The percentage of patients in treatment group C treated at low-volume hospitals should be 26.8%, not 268%.

Reference


γ-Hydroxybutyrate Use in Older Adults

TO THE EDITOR: Background: Use of the “club drug” γ-hydroxybutyrate (GHB), or its precursors γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), is highly prevalent among youths seeking euphoric effects and body builders hoping to increase growth hormone production (1, 2). According to the Drug Abuse Warning Network, 59% of emergency department visits related to GHB involved persons younger than 25 years of age, whereas only 10% of cases involved persons older than 35 (3). Although adolescents and young adults commonly abuse GHB and its precursors, the prevalence of abuse among older Americans is unknown.

Case Report: A 63-year-old man ingested approximately 30 mL of a substance labeled “Chimney Magic” (a chimney cleaning solution) in an attempt to discover its euphoric effects. This product was obtained over the Internet by the patient’s son, who had a history of GHB addiction. The patient subsequently had a witnessed seizure and was unresponsive on presentation. Vital signs included bradycardia (heart rate, 40 beats/min) and hypotension (blood pressure, 80/50 mm Hg). He required mechanical ventilation for 24 hours. Laboratory testing demonstrated a urine GHB concentration of 439 μg/mL. Analysis of the “Chimney Magic” product using gas chromatography mass spectrometry identified GBL as the sole component.

Discussion: Use of GHB, GBL, and 1,4-BD has reached epidemic proportions (1, 3). These drugs are associated with multiple adverse events, including at least 71 deaths (1, 4, 5). After GHB was classified as a schedule I substance in 2000, vendors began selling GBL and 1,4-BD as chemical solvents or dietary supplements, thereby avoiding legal restrictions. Internet drug encyclopedias, such as www.Erowid.com, provide information to potential users on how to obtain and use these substances “safely.” As the erroneous reputation of club-drug safety spreads or as the demographic characteristics of Internet use expand, a corresponding increase in club-drug use in an older population may also occur.

Physicians may encounter patients who ingest GBL or 1,4-BD as dietary supplements named “Verve,” “Jolt,” or “Invigorate.” Doses of these liquid chemicals are measured by using the container cap, which typically holds 5 to 10 mL. The amount of material ingested varies with the users’ intent, but as tolerance develops, the amount and frequency of administration generally escalate. Abstinence may lead to a profound withdrawal syndrome characterized by anxiety, tremors, hallucinations, hypertension, seizures, and, rarely, death (Table) (6).

Clinicians rely on known demographic characteristics and prevalence data to help diagnose disease states. The use of GHB precursors among older adults, although probably uncommon, may stem from their purported health benefits, such as increased growth hormone production and improved energy levels. Low suspicion for club-drug use in older adults may delay accurate diagnosis. Routine qualitative urine toxic screenings rarely assist in management decisions since club drugs—GHB and precursors, ketamine, the hallucinogenic amphetamines 2-CT-7 and 2-CB, and occasionally 3,4-methylenedioxymethamphetamine (also known as “ecstasy”)—are unlikely to elicit a positive response (7). To diagnose GHB, GBL, or 1,4-BD ingestion, urine must be specifically assayed for GHB, most commonly by gas chromatography mass spectrometry. Although serum may be tested, the timeframe of detection is brief, whereas detection in urine is possible up to 10 hours after ingestion (8).

Urine concentrations of GHB in 1 series of acutely intoxicated individuals ranged from 432 to 2407 μg/mL compared with an average of 1.65 μg/mL in controls (a background level generated by the normal metabolism of γ-aminobutyric acid to GHB) (9, 10).

Conclusion: The prevalence of club-drug use, including GHB and its precursors, is increasing in the United States. This report suggests that the demographic profile of club-drug use should include older Americans. Clinicians should remain vigilant for signs and symptoms of club-drug intoxication and withdrawal in patients who do not fit the typical demographic profile.

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References

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute Intoxication</th>
<th>Withdrawal</th>
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</thead>
<tbody>
<tr>
<td>Typical amount ingested</td>
<td>1–5 capfuls, depending on tolerance</td>
<td>History of taking several capfuls daily for weeks to months before drug cessation</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Euphoria, lethargy, coma, hypoventilation, bradycardia, myoclonus</td>
<td>Anxiety, insomnia, tremor, paranoia, auditory or visual hallucinations, mild hypertension, tachycardia, seizures (rare)</td>
</tr>
<tr>
<td>Time course</td>
<td>Onset within 20 min of ingestion, lasting up to 6 h</td>
<td>Onset within 6 h of drug cessation, peaking on day 3, lasting up to 1 wk</td>
</tr>
<tr>
<td>Treatment</td>
<td>Supportive care, often including mechanical ventilation; atropine</td>
<td>Benzodiazepines, baclofen, phenobarbital; patients may attempt self-treatment with ethanol (generally unsuccessful)</td>
</tr>
</tbody>
</table>

Table. Characteristics of γ-Hydroxybutyrate Intoxication and Withdrawal

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events, including death, associated with the use of 1,4-butanediol. N Engl J Med. 2001;344:87-94. [PMID: 11150358]


