Hepatitis C Virus Infections From a Contaminated Radiopharmaceutical Used in Myocardial Perfusion Studies

Priti R. Patel, MD, MPH
A. Kirsten Larson, MPH
Amanda D. Castel, MD, MPH
Lilia M. Ganova-Raeva, MS, PhD
Robert A. Myers, PhD
Brenda J. Roup, PhD, RN, CIC
Katherine P. Farrell, MD, MPH
Leslie Edwards, MHS, BSN, RN
Omana Nainan, PhD†
John P. Krick, PhD
David Blythe, MD, MPH
Anthony E. Fiore, MD, MPH
Jeffrey C. Roche, MD, MPH

Context Nuclear pharmacies prepare radiopharmaceutical products for use in common diagnostic procedures, including myocardial perfusion studies. Hepatitis C virus (HCV) transmission has not been reported previously in the setting of nuclear imaging studies.

Objective To investigate an outbreak of acute HCV infection identified among patients who underwent myocardial perfusion studies on October 15, 2004, using an injected radiopharmaceutical.

Design, Setting, and Patients Outbreak investigation including molecular epidemiology and pharmacy site investigation at outpatient cardiology clinics and a nuclear pharmacy in Maryland. Ninety patients who received injections drawn from select radiopharmaceutical vials prepared on October 14-15, 2004, at a single nuclear pharmacy were offered testing for bloodborne pathogens. Pharmacy procedures were reviewed and HCV quasi species analysis was performed.

Main Outcome Measures Hepatitis C virus infection and quasispecies sequence similarity.

Results Sixteen patients with acute HCV infection were identified from 3 separate clinics. All patients received radiopharmaceutical injections drawn from a single pharmacy vial (vial 1). None of the 59 tested patients who received doses from 6 other vials had acute HCV infection. Blood from a potential source patient with HCV and human immunodeficiency virus (HIV) infection was processed for a radiolabeled white blood cell study in the pharmacy 12 hours before vial 1 was prepared. The HCV quasispecies sequences from this potential source patient were nearly identical to those from cases (97.8%-98.5% similarity). No acute HIV infections were identified. Pharmacy practices that could have led to blood cross-contamination included reuse of needles and syringes during dilutions and use of common flow hoods for some steps in the preparation of sterile and blood-derived products.

Conclusions Sixteen persons acquired HCV infection from a blood-contaminated radiopharmaceutical. The source and practices that could have facilitated breaks in aseptic technique were identified at the pharmacy. Nuclear pharmacies that handle biological products should follow appropriate aseptic technique to prevent contamination of sterile radiopharmaceuticals.
formed in the United States; more than half of these were myocardial perfusion studies.13 Myocardial perfusion studies involve the intravenous injection of a radionuclide (eg, thallium 201 or technetium 99m–labeled sestamibi [Tc 99m sestamibi]), which is detected by nuclear imaging. These radiopharmaceutical products are often prepared in commercial nuclear pharmacies and distributed to hospitals or outpatient clinics for administration.14 Although biological materials are not used in the preparation of radionuclides for myocardial perfusion studies, nuclear pharmacies may process blood for radiolabeled blood cell studies.

In November 2004, 2 older adults with no recognized risk factors for HCV infection were diagnosed with acute HCV infection and reported to a local health department in Maryland. Both patients had symptom onset in early November 2004 and had undergone myocardial perfusion studies at an outpatient cardiology clinic on October 15, 2004. The radiopharmaceutical used was Tc 99m sestamibi, which was prepared by a nuclear pharmacy that also prepared radiopharmaceuticals for other health care facilities in the state. Additional cases of acute HCV infection were subsequently identified among patients who underwent perfusion studies at different clinic sites and who had received Tc 99m sestamibi prepared by the same pharmacy on October 15. The Maryland Department of Health and Mental Hygiene conducted an investigation to determine the mode and extent of HCV transmission.

METHODS

Epidemiological Investigation

All patients who underwent a myocardial perfusion study on October 15 and received Tc 99m sestamibi from the same multidose pharmacy preparation vial as the initial cases (vial 1) were tested for evidence of HCV, hepatitis B virus (HBV), and human immunodeficiency virus (HIV) infection. Using an estimate of the maximum number of doses that could have been prepared from the same multidose saline container used to dilute vial 1, HCV, HBV, and HIV testing were recommended for any patient who received Tc 99m sestamibi from the vial prepared before (vial 0), or any of the 5 vials prepared immediately after vial 1 (vials 2-6). A case was defined as evidence of HCV infection (presence of HCV RNA with either symptoms of acute viral hepatitis or elevated serum aminotransferase levels) in a person who underwent a myocardial perfusion study on October 14-15, 2004.

To determine whether other cases of HCV infection might have resulted from exposures to radiopharmaceuticals prepared by other pharmacies or on different dates, enhanced surveillance for acute HCV cases was conducted. Local health departments in Maryland and infection-control practitioners were contacted to request immediate reporting of all suspected cases and other state health departments were notified through outbreak alerts. Cases reported to the Maryland Department of Health and Mental Hygiene were investigated for recent exposure to nuclear imaging studies. Medical records were reviewed to obtain clinical and laboratory information for potential case and source patients. Demographic information was collected from standard case report forms. Predefined categories were used to collect race/ethnicity information on the surveillance case report forms.

A summary of this public health investigation was submitted to the Science Office in the Office of Workforce and Career Development, Centers for Disease Control and Prevention, for research/nonresearch determination. The Office of Workforce and Career Development Science Office determined that the activities involved in the investigation constituted an urgent public health response and did not require submission of a protocol to the institutional review board.

Nuclear Pharmacy Investigation

A site investigation of the nuclear pharmacy was conducted, including a review of all pharmaceuticals prepared and biologics handled on October 14-15, 2004. The Tc 99m sestamibi and white blood cell (WBC) radiolabeling procedures were observed. Pharmacy employees were screened for anti-HCV, and if positive, were tested for HCV RNA. Employees involved in Tc 99m sestamibi preparation on October 15 or WBC labeling on October 14 were interviewed about their work practices and training.

Review of Radiopharmaceutical Preparation

From our observations, we determined that for each pharmacy preparation of Tc 99m sestamibi, Tc 99m was drawn into a needle and syringe and added to a prefilled manufacturer’s vial of sestamibi powder. Each vial of combined sestamibi and Tc 99m was then heated at 100°C for 10 minutes. Saline drawn from multidose bags or vials was added to dilute the mixture before and after heating. Mixing and dilution were performed by a pharmacist in a laminar flow workstation in a centrally located room of the pharmacy (main room). Following heating, dilution, and assay of each preparation vial of Tc 99m sestamibi solution, individual patient doses (approximately 7-16 per vial) were drawn into syringes by pharmacy technicians in the main room. These prefilled syringes were packaged and delivered to health care facilities for administration.

The WBC radiolabeling procedure was performed by a pharmacist in a designated blood room, adjacent to the main room. For this procedure, whole blood was received and placed in a flow hood to be separated into components. The procedure involved several centrifuge tubes, multiple syringes, and frequent washes of the separated cells using saline from a multidose vial. The procedure also required the pharmacist to leave the blood room carrying the blood-derived preparation to use a hood in the main room where Tc 99m sestamibi and other sterile radiopharmaceuticals were prepared.
Laboratory and Source Investigation

Patient and pharmacy employee serum samples were tested for anti-HCV (Ortho HCV, version 3.0 enzyme-linked immunosorbent assay, Ortho-Clinical Diagnostics, Raritan, NJ). Serum samples from patients and potential source patients (including 3 archived specimens that had been stored at −80°C) were tested for the presence of HCV RNA by qualitative polymerase chain reaction (Amplicor HCV test, version 2.0, Roche Molecular Systems, Branchburg, NJ). Genotypes of HCV were determined using previously described methods. Potentially source patients with undetectable HCV RNA or an HCV genotype that did not match that of the cases were ruled out, leaving 1 suspected source patient.

Patient serum samples were also tested for hepatitis B surface antigen (HBsAg) (ETI-MAK-2, DiaSorin srl, Saluggia, Italy), total antibodies to the hepatitis B core antigen (Bio-Rad Laboratories, Redmond, Wash), and antibodies to HIV (anti-HIV) (Vironostika HIV-1 Microelisa System, bioMerieux Inc, Durham, NC, and HIV-1/HIV-2 Plus O, Bio-Rad Laboratories). Serum samples that tested positive for HBsAg and total antibodies to the hepatitis B core antigen were tested for IgM antibodies to the hepatitis B core antigen (ETI-CORE-IGMK, DiaSorin, Stillwater, Minn) and antibodies to hepatitis B e antigen (ETI-AB-EBK Plus, DiaSorin). Results of serological or RNA tests performed by licensed clinical laboratories were accepted in place of our testing. Follow-up testing for HBsAg was recommended at 4 and 6 months, and for anti-HIV at 4, 6, and 12 months, postexposure for all cases.

The HCV hypervariable region (HVR1) quasi species were isolated and amplified by limiting dilution polymerase chain reaction and sequenced as described previously. Pairwise analysis was used to calculate the distribution of nucleotide variation by using Pileup and Evolutionary Distance programs in the Accelrys GCG Package (Genetic Computer Group, version 10.3, Accelrys Inc, San Diego, Calif). Sequence analysis by different methods indicated similar clustering of sequences. The final neighbor-joining phylogenetic tree was constructed by using Kimura’s 2-parameter model (DNADIST, NEIGHBOR, and DRAWTREE programs of the PHYLP package, version 3.63, Seattle, Wash), and bootstrap analysis was performed to evaluate the reliability of the phylogenetic tree.

RESULTS

Epidemiological Investigation

Sixteen cases were identified; all underwent myocardial perfusion studies on October 15. Cases had perfusion studies performed at 3 unaffiliated clinics (Table 1). The median age of cases was 63 years and 14 (88%) were male. Fifteen cases were symptomatic, including 11 who had jaundice. The median (range) time from exposure to first symptom onset was 24 (15-41) days. One case experienced liver failure and died 10 weeks postexposure; the primary cause of death was sepsis. A second case died from a cerebrovascular event 9 months postexposure. All 16 cases had received injections of Tc 99m sestamibi drawn from vial 1 and were the only patients to have received doses from this vial (Table 2).

A total of 90 patients received injections drawn from vials 0 through 6. Of 74 patients who received injections drawn from vial 0 or vials 2 through 6, 2 were previously known to have chronic HCV infection. Of the remaining 72 patients, 59 (82%) agreed to be tested for anti-HCV and all were negative; 46 (78%) of 59 patients were additionally tested for HCV RNA and all were negative. The attack rate for new HIV (n=54) or HBV (n=53) infections was 0% among patients tested who received injections drawn from vial 0 or vials 2 through 6.

Of the 16 cases, 12 had sufficient HCV RNA for genotyping and were identified as HCV genotype 1a. One case tested positive for total antibodies to hepatitis B core antigen, HBsAg, and antibodies to hepatitis B e antigen, but was negative for IgM antibodies to the hepatitis B core antigen and had radiographic findings suggestive of chronic HBV infection. The remaining 15 cases had no serological markers of HBV infection, and all 16 cases were anti-HIV negative. Follow-up test results were available for 13 of 15 cases who survived for at least 6 months and 10 of 14 cases who survived for at least 12 months postexposure. At 4 to 6 months postexposure, the 13 cases tested negative for markers of HBV and HIV infection. At 12 months, the 10 cases tested negative for anti-HIV.

Pharmacy Investigation

Pharmacy records indicated that 33 vials (approximately 300 doses) of Tc 99m sestamibi were prepared on October 15 (Figure 1). Vial 0 was the last Tc 99m sestamibi vial prepared on October 14; vial 1 was the first vial prepared on Oc-
CONTAMINATED RADIOPHARMACEUTICAL AND HEPATITIS C VIRUS INFECTIONS

Table 2. Selected Vials of Technetium 99m Sestamibi Prepared by the Same Pharmacy, October 14-15, 2004, and Hepatitis C Virus Test Results for Patients Who Received Doses Drawn From These Vials

<table>
<thead>
<tr>
<th>Date Prepared</th>
<th>Time Prepared</th>
<th>Vial No.</th>
<th>No. of Patient Doses</th>
<th>Anti-HCV</th>
<th>HCV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>October 14</td>
<td>7:36 AM</td>
<td>0</td>
<td>3</td>
<td>3 (100)</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1:05 AM</td>
<td>1</td>
<td>16</td>
<td>16 (100)</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1:06 AM</td>
<td>2</td>
<td>15</td>
<td>14 (93)</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1:07 AM</td>
<td>3</td>
<td>16</td>
<td>11 (73)*</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1:08 AM</td>
<td>4</td>
<td>16</td>
<td>13 (81)</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1:09 AM</td>
<td>5</td>
<td>14</td>
<td>9 (69)*</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1:10 AM</td>
<td>6</td>
<td>10</td>
<td>9 (90)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: HCV, hepatitis C virus.

*Excludes patients previously known to have chronic HCV infection (n = 2).

Figure 1. Vials of Technetium 99m Sestamibi Prepared and Blood Procedure Performed in the Same Nuclear Pharmacy by Time, October 14-15, 2004

WBC indicates white blood cell.

October 15. The first 6 vials on October 15 were batched and prepared together, with no more than 5 minutes separating their start times (Table 2).

According to pharmacy records, the only preparation involving blood products on October 14-15 was a WBC-radiolabeling procedure performed on October 14, approximately 12 hours before vial 1 was prepared. A syringe containing 50 mL of whole blood was processed to isolate WBCs and to label them with indium (In) 111 for a WBC scan. The pharmacist who performed WBC radiolabeling on October 14 was not involved in the Tc 99m sestamibi preparation on October 15.

Of 28 employees who were working at this pharmacy in October, 27 were located and agreed to be screened for HCV infection. One employee was anti-HCV positive but HCV RNA negative. This employee had been tested previously and was thought to have resolved infection on the basis of past negative HCV RNA test results. The remaining 26 employees were anti-HCV negative, including the pharmacists who prepared the labeled WBCs and vial 1, as well as the technicians who drew the individual doses on October 15. The employee who could not be contacted had stopped working at the pharmacy on October 8.

Upon inspection of the pharmacy, unwrapped syringes with needles attached were noted in radiopharmaceutical preparation areas, including workstations. Recapping of needles was observed during procedures, and was reported as a routine practice by pharmacy workers. During observed procedures, syringes containing radioactive material were discarded immediately following use, but syringes used to add saline were commonly left in workstations and used for several preparations. Employees reported having received training in radiation safety and aseptic technique. Proficiency in aseptic technique was regularly assessed by growth media challenge tests (a sterile preparation of culture media performed and subsequently observed for microbial growth). Although the pharmacy maintained documentation of reported needlestick injuries, several employees claimed that sharps injuries were not always reported to the pharmacy’s management.

Laboratory and Source Investigation

The patient whose blood had been processed on October 14 (WBC patient) was a nursing home resident with a history of HCV, HBV, and HIV infections, who had been hospitalized for altered mental status and urosepsis. The patient was reinjected with the radio-labeled WBCs prepared by the nuclear pharmacy but was discharged before the imaging scan was performed and died approximately 1 week later. Frozen serum specimens that had been collected from this patient in 1996, 1999, and July 2003 were retrieved. Testing determined that all specimens were HCV RNA positive, genotype 1a.

This patient had previously received antiretroviral therapy for HIV infection but had not been treated for HCV infection. Laboratory studies revealed an HIV-1 RNA concentration of 15 104 copies/mL in August 2004, and an HCV RNA concentration of $1.2 \times 10^8$ copies/mL in May 2000.
2002, the patient tested negative for HBsAg.

Nine of 16 cases had sufficient HCV RNA for quasi species analysis. Quasi species analyses for HVR1 were performed on specimens from these 9 cases and the WBC patient, and compared with 5 NHANES III participants with genotype 1a infection (FIGURE 2). Cases had 2 to 15 distinct HVR1 sequences that were 98.5% to 100% identical to each other. Eleven distinct HVR1 sequences were characterized from the WBC patient specimen collected in 2003. Similarity among the HVR1 sequences in the WBC patient specimen collected in 2003 and the sequences of the 9 cases ranged from 97.8% to 98.5%. The similarity among HVR1 sequences from the WBC patient specimens collected in 1996, 1999, and 2003 was 95.5% to 99.3%. The relatedness of HVR1 sequences from the specimens of cases and the WBC patient compared with the NHANES III specimens ranged from 79.7% to 89.9%. The sequences from the cases and the WBC patient clustered as a group distinct from those of the NHANES III specimens.

**COMMENT**

The findings from this and other recent investigations demonstrate that bloodborne pathogens can be transmitted in any setting where blood exposures occur and aseptic technique is compromised. Health care–related exposures should be considered in the evaluation of patients with acute HCV infection, and clinicians should report these cases to facilitate prompt identification and control of potential outbreaks. This outbreak was detected only after symptomatic patients were reported to a local health department that conducts enhanced HCV surveillance and routinely investigates acute cases. Their investigation of the initial cases identified a common exposure to outpatient cardiology procedures on the same date. The resulting expanded investigation revealed that 16 patients who underwent myocardial perfusion studies at 3 separate clinics acquired HCV infection after receiving Tc 99m sestamibi injections drawn from a single pharmacy preparation vial. Blood from a patient with chronic HCV and HIV infections was the source of HCV transmission, probably through contamination of supplies (syringes or a multidose saline vial) during the preparation of In 111–labeled WBCs on October 14. Although a cost analysis was beyond the scope of this investigation, the costs associated with this outbreak were likely substantial, including those to patients with symptomatic illness that required hospitalization, as well as those incurred by the medical care and public health systems involved. Transmission of HCV from a contaminated radiopharmaceutical has not been described previously.

Multiple lines of evidence support the proposed mode of HCV transmission. Simultaneous transmission to 16 patients occurred in 3 unaffiliated clinics. The attack rate was 100% among patients who received Tc 99m sestamibi from the implicated pharmacy vial and 0% among patients who received doses from the other vials. No pharmacy employee was viremic for HCV. This pharmacy performed no other procedures involving blood products. Furthermore, quasi species analysis demonstrated that the HVR1 variability among the source patient and the cases was less than the variability observed over time within the source patient, as measured at time points spanning 7 years.

Transmission of HCV in health care settings has been linked to failure to adhere to aseptic technique, including reuse of syringes and needles and contamination of multidose medication vials. Although the specific break in aseptic technique that led to transmission was not identified, a number of
observations support the hypothesis that a syringe or multidose saline vial contaminated during the WBC radiolabeling procedure could have been used inadvertently in the Tc 99m sestamibi preparation. First, overlap occurred between areas of the pharmacy where blood components were processed and areas where the Tc 99m sestamibi was prepared. Second, practices that could lead to difficulty distinguishing between used and unused syringes were identified, including unwrapping syringes well in advance of their use, and recapping needles without immediate disposal. Moreover, reuse of syringes was not prohibited. Third, multidose saline vials were frequently used and commonly shared between sterile preparations, and thus could have been a contaminated reservoir.

The exact duration of HCV viability in the environment is unknown. In chimpanzee infectivity studies, HCV in dried plasma at room temperature remained infectious for 16 hours or longer. The timeline that can be constructed from the pharmacy’s records provides additional information regarding HCV viability. Because blood was drawn from the WBC patient approximately 15 hours before preparation of the contaminated Tc 99m sestamibi vial, and cases received injections between 6 and 8 hours later, our findings suggest that HCV at room temperature can remain infectious to humans for at least 21 to 23 hours.

Although the source patient was coinfected with HIV, no evidence existed of HIV transmission. Several factors might explain the absence of HIV transmission in a setting in which HCV transmission was highly efficient. Human immunodeficiency virus is likely less stable than HCV in a room temperature environment and the source patient had received antiretroviral treatment in the past, which might have attenuated HIV transmissibility (a consideration supported by the relatively low viral load in August 2004). Although delayed HIV seroconversion among HCV-infected patients has been reported, no cases had evidence of HIV infection at up to 1 year postexposure.

Nuclear pharmacies are a specialized form of compounding pharmacy regulated by state pharmacy boards and the US Nuclear Regulatory Commission or its state designee. Approximately 370 nuclear pharmacies operate in the United States; most are centralized suppliers, whereas others are hospital-based. Outbreaks of bloodstream infections and meningitis have been attributed to microbial contamination of injected products prepared in compounding pharmacies, raising concerns regarding the adequacy of compounding pharmacy standards, training, and oversight. According to industry observers, comprehensive courses on sterile compounding are not offered at most colleges of pharmacy and many pharmacists have little training in aseptic manipulation skills. Recent surveys of hospital compounding pharmacies have indicated that compliance with quality-assurance guidelines published by the American Society of Health-System Pharmacists remains unacceptably low.

The US Pharmacopeia was recently revised to address pharmaceutical compounding of sterile preparations, including radiopharmaceuticals, and new content has been proposed to address the issue of blood-derived products in nuclear pharmacies. However, no specific information on risk for blood-borne pathogen contamination of compounded pharmaceuticals is provided in the Nuclear Pharmacy Compounding Guidelines from the American Pharmaceutical Association, nor in the model rules for nuclear/radiologic pharmacy of the National Association of Boards of Pharmacy. Furthermore, few explicit strategies aimed at blood-borne pathogen risk reduction are presented in these guidelines or in the US Pharmacopeia. The paucity of guidance on blood manipulation within pharmacies was reflected in this outbreak investigation, which found that training on aseptic technique at the nuclear pharmacy was directed at prevention of microbial contamination and growth, and protocols to address blood-borne pathogen risks appeared limited to worker safety issues rather than the risk of blood contamination of compounded radiopharmaceuticals.

All compounding pharmacies should comply with US Pharmacopeia standards and establish policies to ensure sterile equipment and environments, standardized compounding procedures, and training of employees on aseptic technique. Nuclear pharmacies that handle blood products should additionally recognize the risks for blood contamination of radiopharmaceuticals and implement appropriate precautionary measures to prevent such contamination. The safety of parenteral medications and diagnostic pharmaceuticals depends on careful application of aseptic techniques across the entire spectrum of their preparation and administration. The findings from this investigation, as well as other reported outbreaks, underscore a need for heightened awareness and renewed vigilance.

Author Contributions: Dr Patel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Patel, Larson, Castel, Farrell, Krick, Blythe, Fiore, Roche.

Acquisition of data: Patel, Larson, Castel, Ganova-Raeva, Myers, Roup, Farrell, Edwards, Nainan, Blythe, Roche.

Analysis and interpretation of data: Patel, Larson, Castel, Ganova-Raeva, Roup, Farrell, Nainan, Krick, Blythe, Fiore, Roche.

Drafting of the manuscript: Patel, Castel, Myers, Nainan, Blythe, Fiore.

Critical revision of the manuscript for important intellectual content: Patel, Larson, Castel, Ganova-Raeva, Roup, Farrell, Edwards, Krick, Blythe, Fiore, Roche.

Statistical analysis: Patel, Larson, Castel, Nainan, Roche.

Obtained funding: Farrell.

Administrative, technical, or material support: Patel, Larson, Ganova-Raeva, Myers, Roup, Farrell, Edwards, Nainan, Krick, Blythe, Roche.

Study supervision: Patel, Krick, Blythe, Fiore, Roche.

Financial Disclosures: None reported.

Disclaimer: The findings and conclusions expressed in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Previous Presentation: Presented in part at the 15th Annual Society for Healthcare Epidemiology of America Scientific Meeting, Los Angeles, Calif, April 9–12, 2005.

Funding/Support: This investigation was funded as part of the public health response to an outbreak of hepatitis C by the Maryland Department of Health and Mental Hygiene and the Centers for Disease Control and Prevention.

Role of the Sponsor: The manuscript was reviewed by the Maryland Department of Health and Mental Hygiene and the Centers for Disease Control and Prevention.

Acknowledgment: We thank the following individuals for their contributions to the investigation: Karen Baker, RN, Janice Bolten, RN, Maryellen McManus, RN, MPH, Kelly Russo, MD, MFP, Marie Simpson, RN (Anne Arundel County Department of Health);
REFERENCES


27. Young D. Outsourced compounding can be problematic: community pharmacies linked to contaminated injectables. Am J Health Syst Pharm. 2002;59:2261-2264.


©2006 American Medical Association. All rights reserved.

(Reprinted) JAMA, October 25, 2006—Vol 296, No. 16 - 2011