World of Drug Information

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Goal:
To provide the reader with basic information on viral hepatitis C and its treatment.

Learning Objectives:
1. To recognize viral hepatitis C as a major worldwide health problem.
2. To summarize the most recent literature related to therapeutic treatment options for acute and chronic viral hepatitis C.
3. To recognize viral hepatitis C as a challenge to health care providers.

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Her responsibilities at IDIS include supervision of indexing for the database, indexing articles, providing assistance to subscribers, and maintaining the disease vocabulary.

Viral Hepatitis C: An Overview

Viral hepatitis C is an emerging infectious disease causing a serious worldwide health problem. (World Health Organization, 1999) A potentially fatal disease, hepatitis C virus (HCV) infection is primarily acquired through direct percutaneous contact with blood, blood products or an organ transplanted from a person infected by one of the viruses from the flavivirus family. The hepatitis C virus was isolated and its genome sequenced in the late 1980’s. It is a small fast mutating single-stranded RNA virus with six major known genotypes (1, 2, 3, 4, 5 and 6) and close to 100 subtypes (a, b, c, etc).

The Infection Toll

The toll of infection is high throughout the world. Recent data from the World Health Organization estimates that hepatitis C affects over 3% of the global population — 170 million persons with an additional 3-4 million new cases each year. (World Health Organization, 2000) HCV prevalence varies throughout the world: Europe has the lowest rate (1.03%) while the highest rate (neighboring 5%) is seen in Africa and some Eastern Mediterranean countries. (World Health Organization, 2000) France has 1-1.5% of its population infected with hepatitis C virus and Canada has close to 300,000 persons infected. According to the third National Health and Nutrition Examination Survey (NHANES III) conducted between 1988 - 1994 among U.S. households, 4 million Americans have been infected, 2.7 million of whom remain chronically infected. (Center for Disease Control and Prevention, 2002) The reported incidence of HCV in the U.S. and worldwide could be underestimated due to the exclusion of certain subpopulations from the U.S. survey and the unavailability of prevalence data from several countries of the various WHO regions. Thus, it is difficult to estimate the true incidence of this common chronic bloodborne infection.

In the U.S., HCV is responsible for more than 80% of all non-A non-B hepatitis infections. It is, after alcohol, the second leading contributor to chronic liver disease and may lead to cirrhosis, hepatic failure, and liver carcinoma. Although the estimated number of new acute clinical cases and total new infection cases in the U.S. has been on the decline since the early1990’s (CDC, 2002) , hepatitis C chronic end stage liver disease patients constitute the majority of hepatic transplant recipients. The most recent statistics estimate the annual number of deaths related to hepatitis C to be between 8-10 thousand. The estimated number of new infections and new acute cases for 2001 is respectively 25 thousand and 4 thousand. (CDC, 2002)

HCV prevalence in the general U.S. population is less than 2%.. The population at highest risk of contracting HCV infection is intravenous

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drug users. The use of poorly sterilized needles and syringes accounts for approximately 60% of all HCV transmissions. (CDC, 2002) The risk of acquiring hepatitis C through blood transfusion before 1992 and clotting factors before 1987 was significant. The implementation of mandatory blood donor screening and routine testing of blood products has contributed immensely to the decreased risk of post-transfusional hepatitis in the U.S. The current risk is less than one per million of transfused blood units. (CDC, 2002) An increased risk of contacting HCV infection may also be seen in long term dialysis and transplant patients. Although it is controversial, HCV vertical transmission from an infected mother to her newborn has been reported in the literature. In the U.S. the risk of perinatal transmission is around 5%. Unlike hepatitis B, the risk of contracting hepatitis C by accidental needle stick injury and exposure to contaminated blood in health care workers is low, but a few cases have been reported in the literature. (Sulkowski, 2002) (Alain, 2002) (Yoshikawa, 2000) Transmission through sexual contact is generally rare unless there are additional risk factors involved such as HIV, multiple partners or venereal diseases. Other potential routes of transmission include ear piercing, tattooing and acupuncture. Cases of HCV transmission from an infectious medical staff to a patient have been observed (Ross, 2002) and reports of iatrogenic transmissions due to invasive procedures are found in the literature (Delwaide ,1999) (Esteban, 1996) (Ross, 2000) (Bronowicki, 1997). Ten percent of infected cases have unknown sources of exposure.

The Disease

HCV incubation period spans from 2-20 weeks. On the average 6-7 weeks after exposure, 20–25% of the individuals present with fatigue, anorexia, nausea, malaise, poor appetite or fever. These vague symptoms are frequently not severe enough to seek medical attention. The remaining 75-80% are asymptomatic. Most patients with **acute** hepatitis C have no physical signs of liver disease. Fulminant acute hepatitis C with serious liver problems is rarely seen. The level of serum alanine aminotransferase (ALT), a marker of liver injury, is intermittently highly elevated. Seroconversion occurs 8-10 weeks after exposure. HCV acute infection is, for the most part, undiagnosed, due to its mild nonspecific presentation. Only 10-20% of the people are able to clear the virus within 6 months while the majority remains unknowingly infected and progresses without medical intervention to the **chronic** phase. Chronic hepatitis C course is often silent and variable. Some chronic hepatitis C individuals are asymptomatic up to 25 years; their serum ALT levels are normal and they have no liver disease symptoms. (NIDDK) Some hepatitis C carriers present with intermittent elevated ALT serum levels and mild symptoms of liver disease. One-fifth of hepatitis C carriers have evidence of liver disease characterized by sustained elevation of serum amino-transferase level and presence of HCV RNA in the serum. Hepatic cirrhosis occurs, followed by liver failure and cancer in some patients.

> Some chronic hepatitis C individuals are asymp-tomatic up to 25 years.

Extra hepatic complications such as vasculitis, lichen planus, lymphoma, cryoglobulinemia, fibromyalgia, neuropathy, glomerulonephritis, skin rash and arthritis have been reported in 1% of chronic patients. Overall, HCV is a silent, slowly progressive and serious infectious disease sometimes taking up 2-3 decades before showing its damage.

Treatment and Prevention of Hepatitis C Progression

Prophylaxis and Post-exposure Measures

Unlike hepatitis A and B, for which specific vaccines have proven to be effective, no vaccine is currently available for hepatitis C. The existence of 6 genotypes and close to 100 subtypes combined with frequent mutation in the RNA creating a multitude of "quasispecies" make it difficult to develop a vaccine. Hepatitis A and B immune globulin given as a postexposure prophylaxis for hepatitis A or B has shown a markedly high level of protection (85-90%), but the use of intravenous immunoglobulin as a passive immunization is not supported in hepatitis C. As a postexposure recommendation for health personnel exposed to HCV, the U.S. Public Health Services recently advocated baseline testing for antibodies to HCV and serum liver transaminase levels with subsequent monitoring for progression. (Anonymous, 2001) No post-exposure pharmacological prophylaxis interventions are advised.

Chronic Hepatitis C Therapy

In the 1997 Consensus statement, the National Institutes of Health (NIH) recommended 3 million units interferon alfa (or equivalent) 3 times a week subcutaneously for 12 months as initial treatment in chronic hepatitis C patients with sustained abnormal ALT levels, positive HCV RNA and liver fibrosis or necrosis. (NIH, 1997) If there is no response after 3 months monotherapy, a combination with ribavirin should be considered. Five years later, an updated NIH Consensus Statement provides new directives for the standard of care for chronic hepatitis C (NIH, 2002) recommending a combination therapeutic regimen of pegylated interferon alfa and ribavirin, a recommendation echoed by a French consensus. (ANAES, 2002) A multi-national randomized trial conducted in 1530 chronic hepatitis C patients showed a significantly higher rate of sustained virologic response in patients treated with a combination of peginterferon and ribavirin in comparison with a group of patients treated with standard interferon and ribavirin. (Manns, 2001) Based on the results of 3 pivotal studies, the Food and Drug Administration (FDA) has recently approved Pegasys®, a pegylated interferon alfa-2a, for monotherapy treatment of chronic hepatitis C in naïve adult patients with compensated liver disease. A first pivotal Phase II/III study conducted in 271 chronic hepatitis C patients with compensated cirrhosis or extensive fibrosis showed that 180 micrograms peginterferon alfa-2a given once a week as a monotherapy was significantly more effective than 3 million units of standard interferon alfa-2a administered 3 times weekly in terms of sustained ALT normalization and virologic clearance. Pegylated interferon was as well tolerated as unmodified interferon alfa-2a. (Heathcote, 2000) These results are replicated in a second pivotal Phase III study where 223 chronic hepatitis C patients were given 180 micrograms of pegylated interferon alfa subcutaneously for 48 weeks were compared with 161 patients on interferon alfa-2a (6

> An updated NIH Consen-sus Statement provides new directives for the standard of care

million units of interferon alfa-2a 3 times weekly for 12 weeks followed by 3 millions units 3 times a week for 36 weeks). Assessment done at week 72 supported the use of pegylated interferon in terms of viral clearance (39% of patients versus 19%) and biochemical response (45% versus 25%). The side effect incidence and the rate of drug-induced discontinuation due to adverse effects are similar in both groups (Zeuzem, 2000).

A multicenter randomized controlled study investigated the safety and efficacy of the combination pegylated interferon alfa-2a and ribavirin. (Fried, 2002) Pegylated interferon alfa-2a with ribavirin (180 micrograms pegylated interferon once a week and daily ribavirin) was compared with either weekly peginterferon alfa-2a plus daily placebo, or 3 million units of interferon alfa-2b thrice weekly plus daily ribavirin in 1121 chronic patients for 48 weeks. At 24 weeks post-therapy, pegylated interferon-ribavirin combination provided higher sustained virologic response (56% versus 29% and 44%). The study drug regimen was well-tolerated. Interferon typical side effects were mild to moderate and similar in all three groups although myalgia, fatigue, headache, fever, rigors, and depression rates are lower in patients treated with pegylated interferon.

Acute Hepatitis C Treatment

While several consensus statements and well-defined guidelines have recognized the benefits of interferon alfa, limited data is available for its use in the management of acute hepatitis C and the prevention of the disease progression that can lead to serious liver complications. In light of the above NIH recommendations for chronic hepatitis C, is there a potential role for interferon in acute hepatitis C treatment?

Controlled studies of acute hepatitis C treatment are rare. Currently there is no proven effective treatment. However, a meta-analysis of five randomized controlled and four nonrandomized studies has shown the effectiveness of a short course of low dose monotherapy interferon compared to no treatment. The effectiveness was measured in terms of normalization of serum liver enzymes level (alanine aminotransferase) and serologic clearance of HCV RNA (virologic clearance) at 12 months after the end of the treatment period. (Camma, 1996) Interferon effectiveness is corroborated in a non-randomized prospective pilot study where interferon alfa, given at a higher dose (20 MU daily subcutaneously) to 24 acute symptomatic hepatitis C patients starting from the onset of the symptoms until normalization of serum ALT, prevented chronicity. (Vogel, 1996) The effectiveness of interferons has also been reported in studies of homogeneous populations, i.e. posttransfusion or accidental needlestick acute hepatitis C patients. (Colombo, 1993) (Noguchi, 1997)

...is there a potential role for interferon in acute hepatitis C treatment?

A systematic review of six randomized control trials assessed the therapeutic effectiveness of interferon alfa-2b or interferon beta in 206 acute transfusion-associated hepatitis C patients (Myers, 2002). The control groups had no therapeutic intervention. In three out of the four studies of interferon alfa 2b a standard regimen of 3 millions units interferon alfa-2b units was given 3 times a week for 3 months. The other trial used interferon alfa-2b 3 million units daily for 1 week; 3 million units every 2 days for 11 weeks or 3 million units every 2 days for 12 weeks. Follow-up period varied from 9 -22 months after the end of the intervention. The results of the analysis strongly support the use of interferon alfa-2b in patients with transfusion acquired acute hepatitis C based upon the observation of sustained clearance of viral RNA in the serum and normalization of serum alanine aminotransferase. The results of the two interferon beta trials where a total of 65 patients were treated with 3 million units a day for 5 days with an additional 3 million units 3 times a week for 3 weeks are contradictory and fail to yield conclusive recommendation for the use of interferon beta in acute hepatitis C. The same outcome criteria were used but the follow-up time was 12-22 months.

Review of the literature assessed through the *IDIS* database identified a French consensus conference report which lends support for the use of interferon alfa at a dose of 3 million units 3 times a week for 3 months with an additional 3 month treatment if necessary in acute hepatitis C. (Dhumeaux, 1998)

A recent uncontrolled study reported 98% recovery in 44 acute hepatitis C patients treated with a total dose of 445 million units of interferon alfa-2b (5 million units daily subcutaneously administered for 4 weeks then 3 times a week for the remaining 20 weeks). (Jaeckel, 2001) Recovery was defined as lack of detectable viral RNA in the serum and normalization of the ATL serum levels 24 weeks after the end of therapy. In this study, interferon alfa used as monotherapy effectively prevented the development of chronic hepatitis C. This rate of recovery was extremely high. (Hoofnagle, 2002) The excellent outcome should provide a powerful stimulus for more confirmatory studies to help define the place of interferon in acute hepatitis C and endorse it as “the” pharmacological intervention.

The frequent small sample size of the trials, the different types of interferon used, the dissimilar dose and route of administration, the various modes of infection, the numerous genetic viral variations, the various outcome measures used, the different length of the follow-up periods, and the nature of the disease itself make it difficult to define an optimal regimen capable of ensuring a sustained virologic clearance and normalization of serum liver enzymes levels in patients with acute hepatitis C.

Conclusion

Despite tremendous advances in the understanding and treatment of hepatitis C within the last decade, viral hepatitis C remains a multifactorial challenge for the health care profession.

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ACPE®

Accreditation Information

The University of Iowa College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. The ACPE program number is 020-000-03-001-H01. The Univeristy of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

To earn continuing education credit, complete the assessment exercise, CE registration form and program evaluation, and return to Division of Drug Information Service with a $5.00 check for the processing fee, made out to the College of Pharmacy. A certificate will be awarded upon achieving a passing grade of 70% or better. Pharmacists must complete this program by July 1, 2003 to receive credit.

CE REGISTRATION

TITLE OF EDUCATIONAL ACTIVITY (ARTICLE)

ACPE # 020-000-03-001-H01
VIRAL HEPATITIS C: AN OVERVIEW

NAME ____
ADDRESS ______________________________________
CITY ____________________ STATE __________ ZIP _______
SOCIAL SECURITY NUMBER ______________________________
PHARMACY LICENSE NUMBER(S) __________________________

I HEREBY CERTIFY THAT I HAVE TAKEN THIS TEST:

____
Signature/Date

ASSESSMENT QUESTIONS

(circle the correct answer)

1. Viral hepatitis C is:
   a. A common chronic blood borne infection in the U.S.
   b. pandemic
   c. insidious
   d. all the above

2. Chronicity is the hallmark of viral hepatitis C.
   a. True
   b. False

3. Which of the following statements is accurate regarding viral hepatitis C epidemiology:
   a. Over 3% of people are infected worldwide and Europe has the highest rate of infection.
   b. Over 3% of the world population is infected but the true incidence is not known.
   c. The implementation of blood donor screening and routine testing of blood products has not decreased the number of post-transfusional viral hepatitis C cases in the U.S.
   d. Transmission by accidental needle stick injury accounts for most cases.

4. Due to the high incidence of viral hepatitis C, routine testing is recommended in:
   a. pregnant women
   b. all health care professionals
   c. individuals undergoing acupuncture
   d. none of the above

5. Interferon side effects include:
   a. Myalgia
   b. Depression
   c. Rigor
   d. All the above

6. Which statement describes viral hepatitis C the best:
   a. Viral hepatitis C can be asymptomatic for two to three decades and vague symptoms such as fatigue, anorexia and poor appetite are detected in less than one fourth of the acute cases.
   b. Viral hepatitis C patients have sustained elevated serum alanine aminotransferase indicating liver injury and do not have any extra hepatic complications.
   c. Once infected, an individual cannot mount an immunologic response and spontaneously clear the infection without therapeutic intervention.
   d. Patients with acute viral hepatitis C often have serious symptoms of heptic disease and seek medical advice early in the course of the infection.

7. Intervention recommended by the U.S. Public Health Service for the management of health care personnel with known exposure to hepatitis C virus includes:
   a. Immediate administration of intravenous immune globulin.
   b. Use of interferon upon documentation of exposure to an infected source.
   c. No immediate therapeutic intervention but evaluation of the exposure source and performance of serologic liver enzymes tests together with hepatitis C virus antibody testing and follow up.
   d. Administration of weekly interferon with daily ribavirin upon documentation of exposure to an infected source.

8. Pegasys ® is an FDA approved drug for:
   a. Acute viral hepatitis C in all populations including children.
   b. Chronic viral hepatitis C not responding to a previous treatment.
   c. Chronic viral hepatitis C with compensated liver disease.
   d. Chronic viral hepatitis C only as a combination therapy with ribavirin.

9. Which statement is the most appropriate regarding the treatment of hepatitis C:
   a. Interferon is the back bone of the treatment of chronic viral hepatitis C.
   It is well tolerated and often used in combination with daily doses of ribavirin. It is the recommended drug for chronic viral hepatitis C, but has also a potential role in acute viral hepatitis C therapy.
   b. National and international guidelines advocate the use of interferon and ribavirin combination in all acute hepatitis C patients.
   c. National and international guidelines advocate the initial use of pegylated interferon and ribavirin combination in all chronic hepatitis C patients.
   d. Routine use of hepatitis C immunoglobulin.

10. Viral hepatitis C is a burden and challenge because:
   a. No vaccine is currently available.
   b. No guidelines exist for the treatment of acute viral hepatitis C to prevent its chronicity.
   c. Good epidemiologic data is not available.
   d. All the above.

PROGRAM EVALUATION

	Excellent				Poor
Overall quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
	Agree				Disagree
Important to pharmacists	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me _____ hours and _____ minutes to read this article and complete the assessment questions.

New Drugs: Key References

This new drug selected bibliography provides a selection of key clinical studies and reviews of new drugs approved by the FDA September through November 2002. *IDIS* was searched to retrieve key articles relevant to the new drugs and their approved uses.

Adefovir dipivoxil
Gilson RJ, Chopra KB, Newell AM, et al. A placebo-controlled phase I/II study of adefovir dipivoxil in patients with chronic hepatitis B virus infection, *Journal of Viral Hepatitis.* 1999;6:387-395. ***Adefovir dipivoxil was found to be safe and effective in a randomized, placebo-controlled phase I/II study of 20 patients (13 of whom were also HIV infected), using a once daily 125 mg oral dose of the drug.***

Aripiprazole
Kane JM, Carson WH, Saha AR, McQuade RD, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder, *J Clin Psychiatry.* 2002; 63:763-771.(*IDIS* Article Number 489241). ***Aripiprazole, 15 mg/day or 30 mg/day was compared with placebo and with an active control of haloperidol 10 mg/day in this 4-week, double-blind, randomized trial of 414 patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder.***

Eplerenone
Zillich AJ and Carter BL, Eplerenone—A novel selective aldosterone blocker, *Ann Pharmacotherapy.* 2002;36:1567-1576.(*IDIS* Article Number 487932). ***This article is a comprehensive review of the pharmacology, pharmacokinetics, safety and efficacy of eplerenone.***

Ezetimibe
Gagne C, Gaudet D, Bruckert E, Ponsonnet D, et al. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia, *Circulation.* 2002; 105:2469-2475.(*IDIS* Article Number 482036). ***In this 12-week, double-blind trial evaluating the safety and efficacy of ezetimibe, 50 patients were randomized to atorvastatin or simvastatin 80 mg/day; ezetimibe 10 mg/day plus atorvastatin or simvastatin 40 mg/day, or ezetimibe 10 mg/day plus atorvastatin or simvastatin 80 mg/day.***

Bays HE, Moore PB, Drehobl MA, Rosenblatt S, et al. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: Pooled analysis of two phase II studies, *Clin Ther.* 2001; 23: 1209-1230. (*IDIS* Article Number 469323). ***Data from two phase II placebo-controlled, double-blind randomized trials were pooled to assess the efficacy and tolerability in a total of 432 patients for 12 weeks of ezetimibe given in once daily doses of 0.25, 1, 5, or 10 mg or placebo in Study A, or 5 or 10 mg or placebo in Study B.***

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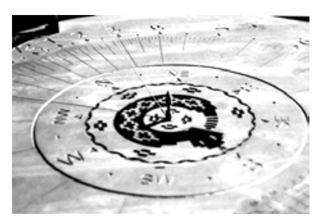
2003 RENEWAL REMINDER

By now you should have received your 2003 renewal notice. Please let us know if you have not received it. We urge you to notify us of your renewal intentions as soon as possible. To avoid interruption of service, we need to receive your renewal form by January 1, 2003. Thank you for your prompt attention to your 2003 *IDIS* subscription renewal.



FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) Trade Name	Sponsor (Approval Date)	Valid IDIS Drug Term Drug Number (IDIS Citations)*	Indication/Use	Valid *IDIS* Disease Term Modified ICD-9-CM Number
Adefovir Dipivoxil (1P)***** *Hepsera*	Gilead Sciences, Inc. (Sept. 20)	ADEFOVIR 8180082 (15 citations)	For the treatment of chronic hepatitis B in adults with evidence of active viral replication and either elevations in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or histologically active disease.	Hepatitis, Viral B 070.2
Aripiprazole (1S)*** *Abilify*	Otsuka Pharmaceutical (Nov. 15)	ARIPIPRAZOLE 28160846 (2 citations)	Schizophrenia.	Schizophrenia NEC 295.
Eplerenone (1S)*** *Inspra*	Rx G.D. Searle LLC (Sept. 27)	EPLERENONE 40280050 (2 citations)	For treatment of hypertension.	Hypertension 401.
Ezetimibe (1S)*** *Zetia*	MSP Singapore Company, LLC (Oct. 25)	EZETIMIBE 24060018 (9 citations)	Primary hypercholesterolemia: as monotherapy or in combination with an HMG-CoA reductase inhibitor. Homozygous familial hypercholesterolemia: in combination with either atorvastatin or simvastatin. Homozygous sitosterolemia.	Hypercholesterolemia, Pure 272.0

*   Through November 2002 Update. Complete bibliographic citations will be provided upon request.
**   Not applicable.
***   New molecular entity given standard review by FDA.
**** Designated orphan drug.
***** New molecular entity given priority review.

Additional information on these newly approved drugs will be available in the FDA Approval Package [an official United States Food and Drug Administration (FDA) document] that is compiled for new drugs following approval. This document includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are indexed and included as part of the *IDIS* database. Use descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the database.

Perspective from an *IDIS* Subscriber

New onset lower extremity weakness, unsteady gait, and imbalance: Possible peripheral neuropathy associated with use of a HMG-CoA reductase inhibitor or fibrate?

DATA:

ALLERGIES/ADVERSE DRUG REACTIONS—penicillin-rash and itching; contrast-red "all over;" simvastatin and gemfibrozil-myositis. VITALS—(10/16/02) temperature 98.5, pulse 87, respiratory rate 18, blood pressure 132/72. MISCELLANEOUS—(10/16/02) age 77 years, weight 205 lbs, height 66 inches. LABS—(10/18/02) sodium 140, potassium 4.7, (blood urea nitrogen) BUN/s. creatinine 31/1.5, liver function tests - within reference ranges, calculated creatinine clearance 43ml/min.

HISTORY OF PRESENT ILLNESS:

SOCIAL: Since his wife's death four years ago, JB lives alone on the 8th floor of an apartment building. He is visually impaired, but his corrected vision is adequate for normal daily activities. He does his own shopping and cooking, but does not drive. He manages his own medications.

MEDICAL:

JB has multiple medical problems, but had no new complaints since his Coronary Artery Bypass Graft almost two years ago. Six months ago he reported walking a mile a day without difficulty. His long standing foot pain syndrome began between five and ten years ago in his left foot and within one to two months had spread to include his right foot. He had no numbness in his feet in the beginning. The foot pain was present only on the dorsal surface of his feet. The intensity of the foot pain syndrome gradually increased up to a level of five on a ten point scale and remained stable for several years until the past twelve to twenty-four months when his foot pain increased to a level of seven on a ten point scale. JB states that until a month or two prior to his admission to another hospital in March of this year he had used a cane primarily because of visual problems, not because of balance problems or difficulties with walking. Simvastatin 10mg at bedtime was added to a gemfibrozil regimen for lipid control on February 5, 2002. Within one to two weeks of starting the simvastatin JB reported a new syndrome of difficulty rising from a seated position, a very unsteady gait with episodes he described as "staggering" and the inability to stand still without support. He denies any similar balance or gait problems in the past. Several days into an eighteen day hospital admission both the simvastatin and gemfibrizil were discontinued because of "myositis." Within a few days he noticed improvement and during the last week of the admission the syndrome of impaired balance was markedly improved and his lower extremity weakness was described as about 80% improved. At the time of his discharge he was walking for ten to fifteen minutes in the hospital hallways without assistance. During this period his long standing foot pain syndrome was unchanged. Within two days of discharge (05/07/02) JB described the acute return of the syndrome. The syndrome gradually worsened until around early September. He had been prescribed fenofibrate 160mg at bedtime on July 30th. He had not taken the medication as of September 2nd because of fear of the return of the "myositis." The fenofibrate was actually started in the first week of September. He was admitted to our unit on October 16, 2002 with a chief complaint of weakness in his legs which has limited his daily activity. He also continued to complain of severe pain in his feet unrelieved by his current regimen. He reported brief periods of foot pain relief in the past when opioids were used.

PHYSICAL EXAMINATION: SELECTED FINDINGS

(10/16/02) NEUROLOGICAL: Motor Strength: 5/5 upper extremities, Lower Extremities: hip extension 4/5, hip flexion 3/5, knee flexion 3/5, knee extension 4/5, plantarflexion 4/5, dorsiflexion 3/5, SENSORY: vibration sense absent below the knees, light touch absent in big and little toes, patellar and Achilles reflexes absent bilaterally, marked atrophy of calf muscles and some atrophy of thigh muscles.

PAST MEDICAL HISTORY:

Coronary artery disease (status post Coronary Artery Bypass Graft 10/00, status post myocardial infraction x 3 by history in 1973,1976 and 2000), diabetes mellitus type 2, heart failure, hyperlipidemia, peripheral neuropathy, orthostatic hypotension by history, obesity, deep venous thrombosis after surgery, multiple eye surgeries, acquired myopathy, impaired balance.

EDITORS NOTE:

FROM TIME TO TIME, WE PUBLISH ARTICLES CONTRIBUTED BY IDIS SUBSCRIBERS. AN ARTICLE FROM DAVE MACE, B.S.PHARM., IS INCLUDED IN THIS ISSUE. DAVE MACE IS FROM AN INSTITUTION THAT IS A LONG-STANDING IDIS SUBSCRIBER, UTILIZING THE DATABASE ON A REGULAR BASIS. HIS CONSULT ILLUSTRATES IDIS DATABASE USE CONTRIBUTING DIRECTLY TO PATIENT CARE OUTCOMES. THE RESPONSIBILITY FOR ERRORS IS THE AUTHOR'S ALONE. THE CONSULT DOES NOT NECESSARILY REPRESENT HOSPITAL VIEWS AND RECOMMENDATIONS. WE HOPE YOU FIND THE INFORMATION INTERESTING AND USEFUL AND WELCOME COMMENTS. IF YOU ARE INTERESTED IN SHARING YOUR EXPERIENCES USING THE IDIS DATABASE, PLEASE CONTACT DONNA-BRUS@UIOWA.EDU

MEDICATIONS:

On admission: propoxyphene 65mg three times daily, gabapentin 300mg three times daily, fenofibrte 160mg at bedtime, salsalate 500mg three times daily when necessary for pain, lorazepam 1mg at bedtime, acetaminophen 500mg three times daily, aspirin enteric coated 325mg once daily, vitamin E 400 international unit once daily, docusate 100mg three times daily, glyburide 5mg every am, furosemide 40 mg once daily or two times daily as needed, potassium chloride 8 milliequivalents once daily when taking furosemide twice a day.

LITERATURE:

Recently Gaist and colleagues (2002) published a case control study of statins and the risk of polyneuropathy in 465,000 inhabitants of Funes county Denmark. Patients with concurrent diagnoses of diseases which predisposed them to polyneuropathy were excluded. The remaining polyneuropathy codes were matched with prescription records. They identified 166 cases with a first time diagnosis of idiopathic polyneuropathy. Nine cases had been exposed to statins with a median duration of use of 2.8 years, only two had taken statins for less than twenty months. The odds ratio of polyneuropathy was 4.6 (95% CI 2.1 to 10.0) if all cases were included. If only definite polyneuropathy cases were included the relative risk increased to 16.1 (5.7-45.4). The toxic polyneuropathy seems to occur most often after long-term treatment with a statin.

Previously the same group had published a cohort study based on information from general practices in the United Kingdom that suggested statin therapy might be associated with peripheral neuropathy. The incidence of peripheral neuropathy among users of lipid-lowering drugs was 0.7 per 10,000 person-years. The two confirmed cases of peripheral neuropathy in the treated cohort were both current users of simvastatin. In both cases their polyneuropathy symptoms resolved after the drug was discontinued. The relative risk of peripheral neuropathy was not increased in the non-treated hyperlipidemic cohort and was identical to that of the background population. Their results suggest one excess case of neuropathy for every 14,000 years of statin therapy. (Gaist, 2001)

CASE REPORTS - FIBRIC ACID DERIVATIVES

Corcia and colleagues (1999) described a 60 year-old male with leg pain for six months. He had been taking fenofibrate 200mg daily for five years. He reported paresthesia in the posterior aspect of both thighs with subsequent progressive muscle weakness. On physical examination he could not stand on his toes or heels. There was no proximal muscle weakness or sensory loss. Electromyogram results included reduced amplitude of nerve action potentials without any slowing of conduction velocity consistent with axonal degeneration. The fenofibrate was discontinued and within three months his walking distance had improved, within seven months his distal muscle strength had improved and his muscle pain had resolved.

Ellis and colleagues (1994) published the first report of peripheral neuropathy associated with bezafibrate therapy, supported by nerve conduction studies. They describe a previously well 52 year-old male who started taking bezafibrate 200mg three times daily two months after a myocardial infarction. One month later he developed a persistent painful tingling in his fingers and toes, which became progressively worse over six months. No weakness was reported or present on examination. He had lost all sensation in a stocking and glove distribution to mid calves and wrists bilaterally. His ankle reflexes were depressed. Nerve conduction study results were within normal limits. Bezafibrate was discontinued and the symptoms completely resolved. They included less well documented reports from various monitoring programs: (New Zealand - three reports) (British - five reports) (WHO four reports of neuropathy, thirteen of paresthesia) and the drugs manufacturer's safety department (seventeen reports).

Kanterewicz and colleagues (1992) had previously reported a case of bezafibrate associated rhabdomyolysis. A 70 year-old female had been on bezafibrate 400mg twice daily for forty days prior to her admission for recurrent angina. Eight days after admission she suddenly developed diffuse thoracic and upper limb pain. Her electrocardiogram showed no evidence of acute infarction. Her creatinine kinase levels were high 6480 international unit/L; the MB fraction was 1.9%. The ninth day after admission she presented with profound muscle weakness and muscular cramps. Her limb muscles were painful on examination. Her urine was reddish and urine test strips showed positive hemaglobin with no cells visable in the urine. One week after bezafibrate was discontinued she was asymptomatic. Two weeks later her creatine kinase value had returned to normal. She was followed up six months later and remained well without any muscular symptoms.

Kanterewicz and colleagues also included data from eight other cases of bezafibrate associated myopathy from German language publications. They also referenced a review of the literature by Rush in Seminars in Arthritis and Rheumatism published in1986 describing seventy-eight cases of clofibrate associated myopathy. In the Rush review forty-three of sixty-four cases reported muscle pain and thirty-two of forty-five cases reported weakness. No information was provided about the resolution of the syndrome when clofibrate was discontinued. Additional cases of colfibrate associated myopathy include those reported by Rumpf and colleagues (1976) and Langer and Levy (1968).

Interestingly two case reports of clofibrate associated myopathy also included signs and symptoms consistent with a peripheral neuropathy. Gabriel and Pearce (1976) described a twenty-five year old chronic renal failure patient on twice weekly dialysis, who reported weakness in his legs after seven months of therapy with colfibrate, one gram daily in divided doses. After thirteen months he reported diffuse pain in his legs and soreness of the soles of his feet. Nerve conduction studies suggested a mild motor neuropathy of the lower limbs. Colfibrate was withdrawn and over the next sixty days the signs and symptoms resolved.

Katsilambros and colleagues (1972) described a thirty-six year old female with diabetes mellitus since age ten with clinical evidence of retinopoathy and nephropathy. Therapy with clofibrate 500 mg four times daily was started after a heart attack. Thirteen months later she was admitted to hospital with a six month history of general muscle aches in the thighs, and muscle weakness which progressed to the complete inability to walk. Reflexes were absent and vibratory and pinprick sensation were impaired. The lower extremities were most affected. Within two days of withdrawal of clofibrate there was a sharp decline in her creatine kinase values, which had returned to normal within two weeks. There was no clinical recovery following withdrawal of the clofibrate.

CASE REPORTS – HMG-CoA REDUCTASE INHIBITORS

Jeppesen and colleagues (1989) reported seven cases of peripheral neuropathy associated with long term hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) therapy from an academically based neurology department. Four of the cases appear to be irreversible. This case series includes individual results of the neurologic examination, nerve conduction studies, and quantitative sensory testing. The duration of statin therapy prior to emergence of the neuropathy ranged from one to two years to six years. Only two cases described muscle weakness in addition to varied sensory disturbances.

Phan and colleagues (1995) described four patients who developed a syndrome of sensory and or motor changes that developed from within days to two years after starting simvastatin therapy. Three of the cases had both sensory and motor symptoms and one had only pain and parasthesia. In each case there was symptomatic improvement after the simvastatin was withdrawn. They also included comments on thirty-eight other cases which had been previously reported to the Australian Adverse Drug Reactions Advisory Committee with symptoms suggestive of peripheral neuropathy associated with simvastatin use. In twenty-two of the thirty-eight cases the patient recovered after simvastatin was discontinued and in five cases there was a positive rechallenge after the drug was restarted.

Ziajka and Wehheier (1998) described a patient who developed peripheral neuropathy several years after starting lovastatin therapy. There was partial resolution of the syndrome when lovastatin was withdrawn. Subsequent rechallenges with pravastatin, simvastatin, niacin, and atorvastatin all resulted in a return of the neuropathic pain syndrome, that improved when the drugs were withdrawn.

Other cases of lovastatin peripheral neuropathy have been published by Ahmad (1995), Jacobs (1994), and one case from the lovastatin five year safety study in 745 patients. (Davignon et al. for Lovastatin Study Group, 1993).

COMMENT:

The voluntary withdrawal of cerivastatin (Baycol™) from the U.S. market on August 8, 2001 by the manufacturer in agreement with the FDA has focused attention on the occurrence of myalgia, myositis, or rhabdomyolysis in patients on HMG-CoA reductase inhibitors or a combination of one of them with a fibric acid derivative. The American College of Cardiology, the American Heart Association, and the National Heart, Lung and Blood Institute have jointly published a clinical advisory on "the use and safety of statins." (Pasternak, 2002) They do not include any information on peripheral neuropathy as an adverse effect of the HMG-CoA reductase inhibitors or fibric acid derivatives.

For further information on peripheral neuropathy the reader is referred to recent reviews by Hughes (2002), Barohn (1998),and McLeod (1995).

In this case the rapid onset of impaired sensation, weakness and balance syndrome after simvastatin was started and their almost complete resolution within seven to ten days after simvastatin and gemfibrizol were withdrawn is consistent with the published literature. The natural history of such syndromes after drug withdrawal is incompletely described.

The unexplained worsening of his syndrome after hospital discharge while the patient was reportedly not taking lipid lowering therapy and the repeated worsening after return from a recent pass is problematic. The role of his diabetes or other etiologies in this syndrome remain unclear.

Both statins and fibric acid derivatives have been associated with syndromes of myopathy/myositis/ rhabdomyolysis and peripheral neuropathy. He is currently on fenofibrate. He currently complains of lower extremity weakness and balance problems similar to those he

Dave Mace, R.Ph., Drug Information Specialist, wrote the article. Mace graduated from the University of Iowa College of Pharmacy in 1967. Since 1982 he has served as the Director of the Drug Information Center at BPVAMC, 10,000 Bay Pines Blvd., Bay Pines, FL 33744. His responsibilities include serving as a preceptor for drug information and Pharm.D. clerkship programs and responding to complex drug information requests from clinical staff.

experienced previously, after simvastatin was added to his regimen this spring.

Nerve conduction studies are done twice weekly at our institution. If they are consistent with anoxal degeneration a trial of fenofibrate is recommended. The time frame for improvement after drug withdrawal is not clear. Some cases have seen improvement within days or a week, other cases have taken several months to improve and in some cases there has been no improvement. The recent literature suggests that toxic neuropathy temporally associated with the use of lipid-lowering therapy is more common than suspected. It may emerge as another significant toxic syndrome associated with the use of HMG-CoA reductase inhibitors and fibric acid derivatives.

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RUTH CALLOWAY RETIRES

Dean Cohen presenting chair to Ruth Calloway

Since the Spring of 1983, Ruth Calloway, R.Ph., M.S. has been a member of the Division of Drug Information Service staff. A respected and proficient contributor to the *Iowa Drug Information Service* database, Ruth oversaw the *IDIS* drug vocabulary file. Her insight into drug development and nomenclature ensured the validity of the entries and ease with which the vocabulary can be accessed by *IDIS* users. Additionally, Ruth, through her teaching, revealed the worth and foibles of drug information resources to many B.S. and Pharm.D. students. At a reception in November 2002 the College of Pharmacy honored Ruth and her contributions to teaching and service. Dean Jordan Cohen presented her with a chair with the University seal.

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