

Possible Pandemic Threat on the Horizon – Avian Influenza A (H5N1)

Learning Objectives

1. Understand the history of avian influenza that has led to the concerns about what could develop in the near future.
2. Describe the host-vector transmission relationship of the current virus of concern (H5N1), the highly pathogenic avian influenza virus.
3. List the laboratory tests and symptoms for the diagnosis of avian influenza.
4. Explain how patients with documented infection are treated and how their care is managed.
5. Describe the options available for prevention of the disease following exposure to infected animals and prevention measures worldwide to avert a pandemic of avian influenza.

About the Authors:



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Dr. Herman graduated from the University of Iowa College of Pharmacy in 1976 (B.Sc.), 1978 (M.Sc. Clinical/Hospital Pharmacy) and 1992 (Ph.D. Pharmacokinetics). He is an Associate Professor (Clinical) at the College of Pharmacy in the Division of Drug Information Service where he is director of the Iowa Drug Information Network and is involved with didactic and clerkship teaching in the Clinical and Administrative Pharmacy Division. Melissa Storck is a 2006 Pharm.D. candidate from the University of Iowa College of Pharmacy and will be graduating in May 2006. She aspires to be a clinical pharmacist and is pursuing a pharmacy practice residency in the state of Florida to achieve this goal.

Introduction

During the past few months, avian influenza A (H5N1), or H5N1 highly pathogenic avian influenza (HPAI),^{1,2} has become the center of the world's attention because of the possibility of a global pandemic. Currently, millions of birds, many of them chickens, have either died from avian influenza or been slain to contain or delay the spread of the source to other birds, and possibly to humans.³

The World Health Organization (WHO) reports the number of laboratory-confirmed cases and deaths of bird flu in humans and as of December 7, 2005 nearly 135 cases of HPAI have been identified and approximately 50% of these cases have lead to death.² The current countries that have reported human cases of bird flu are Indonesia, Vietnam, Thailand, and Cambodia. Positive tests for HPAI in birds have occurred in: Indonesia, Turkey, Russia, Kazakhstan, Mongolia, China, Thailand, Cambodia, Vietnam, Republic of Korea, Japan, Malaysia, and possibly Romania.¹ The WHO classifies the pandemic threat into six phases⁴ and currently the level is stable at phase 3: "a virus new to humans is causing infections, but does not spread easily from one person to another".⁵ A summary of the history, transmission, diagnosis, treatment and prevention of avian influenza will be presented.

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PERSPECTIVE FROM AN IDIS SUBSCRIBER: METFORMIN AND NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM): WHEN, IF EVER, ARE USERS AT RISK OF DEVELOPING LACTIC ACIDOSIS?

History

There are many subtypes of avian influenza and the three of greatest concern are H5, H7, and H9.⁶ These are worrisome because these subtypes have been transmitted to humans from poultry, with H5N1 being the most pathogenic, but H7N7 and H9N2 are also of concern.⁷ In 1997, a total of 18 people were diagnosed in Hong Kong with H5N1 infection and 6 of these patients died. All the poultry in Hong Kong were eliminated, which halted the threat of an outbreak. H5N1, however, continued to be present in birds in China, and, in 2002, it appeared again in Hong Kong with a slightly different genotype than what was isolated in 1997. The 2002 outbreak was extremely virulent in ducks and aquatic birds, which is a characteristic that is rarely correlated to HPAI viruses. In 2003, a father and son in Hong Kong were infected with the H5N1 virus, and the father eventually died. The daughter also came down with an unidentified respiratory disease and died, but the pathogen was not identified.

Two different genotypes of the HPAI H5N1 virus were identified during 2003-2004 resulting in enormous outbreaks in Vietnam, Thailand, Indonesia, Cambodia, Laos, Korea, Japan, China and Malaysia.⁷ Even though the outbreak was mainly limited to chickens, there was transmission of the virus to humans. The WHO reported 44 cases and 32 of these resulted in death.² Virus-containing isolates were taken from Vietnamese victims and it was found that the virus was resistant to amantadine and rimantadine.⁷

Since December 2004, 72 additional cases have been confirmed by the WHO, 28 of which have resulted in death.² It appears that H5N1 is moving to other countries, and new cases in birds and humans are arising more frequently.

Transmission

The majority of the cases of HPAI in humans has been following transmission of virus from birds to humans.⁸ Wild birds are most frequently infected with avian influenza A virus, but domestic birds including chickens and ducks have increasingly become infected. When the outbreak in humans occurred in 1997, infected patients had been exposed to direct contact with ill poultry or their excrements or had been involved with

killing infected poultry within one week of having any symptoms. There did not appear to be any risk associated with eating poultry products or being exposed to a person who was infected with H5N1.

Evidence regarding direct human-to-human transmission of HPAI H5N1 is sparse. Serologic studies were performed on health care workers that took care of ill patients, and it was found that the virus cannot spread effectively between people.⁸ However, there is one suspected case of possible human-to-human transmission in a family during the outbreak of 2004 in Thailand.⁹ An 11-year-old girl who lived with her aunt was admitted to a hospital on September 7, 2004, with an upper respiratory illness and fever. Diseased chickens lived at the house with the girl and her aunt. Her symptoms began 3-4 days after her last exposure to the chickens. The girl progressively got worse, and her mother, who came from a distant city, and aunt provided bedside care for the girl around the clock. The girl died on September 8, and on September 17 the mother was admitted to a hospital in her city with a respiratory illness; she died on September 20. On September 16, the aunt reported influenza symptoms and was admitted to the hospital on September 23 with respiratory difficulties. This time, the hospital team suspected avian flu and treated her with oseltamivir. The aunt recovered and was released on October 7. Investigation into this case found that the mother had no exposure to poultry in her hometown and none on her way to the hospital. The aunt kept chickens at the house in which the girl was exposed, but the chickens died on August 29 and 30 after having an unidentified illness. The aunt had not had contact with any chickens after those dates and her symptoms did not begin until the 16th. The usual incubation period of the virus is 2-4 days after exposure, but has been reported up to 8 days.⁸ Tests for influenza A (H5N1) were done on the mother's tissue obtained through an autopsy, and on nasopharyngeal and throat swabs from the aunt.⁹ These tests came back positive for both women. The investigators concluded that the most plausible reason the mother and aunt contracted the illness was during close personal contact with

the child when they cared for her while she was dying.

Human-to-human transmission is possible with close contact of an infected child, but it is not highly likely at this point based on previous studies where there was no aerosolized transmission between humans.^{7,8} H5N1 has high affinity for a specific amino acid linkage on avian RNA but does not readily establish this same linkage on human RNA, thus, it is very difficult for humans to become infected. The possibility of a new H5N1 subtype that can lead to highly efficient human-to-human transmission is very real.¹⁰ There are a few ways a new human subtype can evolve: 1) the virus can infect humans and undergo adaptive mutations that allow it to recognize the linkage on human RNA, or it could obtain genes from a human influenza virus that would allow it to replicate effectively in humans, or 2) both an avian flu virus and human virus are present in a third host and then "mix" together. Ito and coworkers¹¹ suggest that pigs have both linkages, so they can be infected by both avian and human influenza A virus at the same time. It is theoretically possible for the avian flu virus to adapt the human linkage or acquire genes from the human virus while residing in the pig.¹² This mutation could result in a new virus subtype that would be able to have efficient human-to-human transmission while retaining the virulence of the avian influenza.

Laboratory Tests

Patients with the human influenza virus are generally diagnosed using nasal samples; however, throat samples may provide better results for the detection of avian influenza. In order to confirm the presence of H5N1, one or more of the following lab tests must have positive results: a viral culture, a polymerase chain reaction (PCR) assay for influenza A (H5N1) RNA, an immunofluorescence test for antigen with the use of monoclonal antibody against H5, and at least a fourfold rise in H5-specific antibody titer in paired serum samples.⁸

Detection of viral RNA in the samples may take anywhere from 2-15 days from the initial onset of symptoms.

Symptoms

Some of the symptoms that patients experienced in 1997 were not as prevalent as they are in H5N1 patients today.⁸ Most patients today present with a fever (temperature >38°C), cough, shortness of breath and an increased respiratory rate. Diarrhea, vomiting⁸ and hypotension¹³ have also been recorded. The majority of patients in the more recent infections also have pulmonary infiltrates and other pulmonary changes.⁸ Lymphopenia, thrombocytopenia and increased aminotransferase levels are relatively common. As the infection progresses, many patients experience respiratory failure and other organ dysfunction. The mortality rate appears to have increased since 1997. It was 33%⁸ then and is approximately 50%² now. There is the possibility that milder cases are going undiagnosed, and the sample size is relatively small so this may not be a true increase.⁷

Management/Treatment

Currently, there are 4 antivirals for the prophylaxis or treatment of human influenza: amantadine, rimantadine, zanamivir (Relenza[®]) and oseltamivir (Tamiflu[®]).⁴ The proposed mechanism of action of both amantadine and rimantadine is inhibition of viral replication; however, the full action is not understood completely.¹⁴ Currently, the Center for Disease Control (CDC) advises that these 2 medications only be used for the prophylaxis of human influenza, not avian influenza (H5N1). The H5N1 subtype that is circulating today appears to be resistant to both amantadine and rimantadine.⁸ Zanamivir and oseltamivir are neuraminidase inhibitor antiviral agents. Like amantadine and rimantadine, these agents also inhibit viral replication, but it is by a different mechanism. Neuraminidase releases the virus from the host cell. Neuraminidase inhibitors prevent this from occurring.¹⁴ This provides a theoretical basis for these agents to be used for the treatment of

HPAI H5N1. Although anecdotal reports exist, no formal studies have been conducted to evaluate zanamivir or oseltamivir as treatment for avian influenza A (H5N1). However, in-vitro studies have shown this virus to be susceptible to both oseltamivir and zanamivir; thus, one or the other should be given early in the treatment of patients with possible H5N1 infection.⁸ The possibility exists for the virus to become resistant to these agents. Only 1 amino acid of the protein N1 neuraminidase would need to be substituted for resistance to occur. Other agents under investigation for the treatment of H5N1 are peramivir, long-acting topical ribavirin and interferon alfa.

Patients hospitalized with H5N1 infection have received other treatment as well. Supportive care is the mainstay of treatment.⁸ Most patients require supplemental oxygen and/or ventilatory support and intensive care for multiorgan failure. Ten H5N1 infected patients in Vietnam received broad-spectrum antibiotics, and the majority were treated with a corticosteroid and an antiviral.¹³ Even though corticosteroids have been used in most patients, their role in the treatment of H5N1 is uncertain.⁸

Prevention

There are no vaccines available at this time for the prevention of avian influenza H5N1 infection. The National Institute of Allergy and Infectious Diseases (NIAID) announced in March 2005 that they were going to begin an investigative trial to study the safety of a new H5N1 vaccine.¹⁵ Two pharmaceutical manufacturers, Sanofi Pasteur and Chiron, are developing vaccines that will be tested in Phase I trials conducted by NIAID.¹⁶

The WHO recommends that people who have possibly been exposed to infected birds or humans should receive prophylactic treatment with 75 mg of oseltamivir once daily for 7 to 10 days.⁸ If it appears that a new H5N1 subtype has developed and is transmitted from human-to-human more easily, then preexposure prophylaxis may need to be considered.¹² Individuals who have had a possible exposure should self-

quarantine themselves for at least 1 week after the exposure.⁸

In order to keep HPAI H5N1 from entering this country, the USDA's Animal and Plant Health Inspection Service (APHIS) oversees the maintenance of "trade restrictions on the importation of poultry and poultry products from affected countries."¹⁷ To prevent and prepare for a possible pandemic the CDC is providing the leadership required for the National Pandemic Influenza Preparedness and Response Task Force. They are also working closely with other groups, such as the Association of Public Health Laboratories, the Council of State and Territorial Epidemiologists, the Department of Defense, the Veterans Administration, the WHO, and the Vietnamese Ministry of Health. The collaboration of all these groups will allow for more effective preventative measures and planning of the necessary steps in the event of a pandemic.³

Conclusion

There have been no reported cases of HPAI H5N1 in the United States as of December 7, 2005. More and more cases of avian influenza A (H5N1), have been found in birds in numerous countries and the virus appears to be moving west. The virus is not transmitted efficiently from birds to humans so the threat to the human population is not currently great. Even though this is the case now, there is a real possibility for the virus to mutate, and its ability to transmit from person to person could increase rapidly. The WHO, CDC, and other groups are working diligently to keep the situation under control and the virus from spreading to other parts of the world. Hopefully, these and future efforts will prevent a potentially devastating outcome.

References

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Accreditation
Information



The University of Iowa College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. The ACPE program number is 020-999-05-097-H01. The University 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 on page 6, and return to Division of Drug Information Service with a \$7.50 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. Please allow up to 4 weeks for processing. Pharmacists must complete this program by December 21, 2008 to receive credit.

CE REGISTRATION

ACPE# 020-999-05-097-H01 (1 CEU/1 Hr.)

VOLUME: 16 ISSUE: 4 DECEMBER 2005

TITLE OF EDUCATIONAL ACTIVITY (ARTICLE)

POSSIBLE PANDEMIC THREAT ON THE HORIZON-AVIAN
INFLUENZA A (H5N1)

NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

SOCIAL SECURITY NUMBER (OPTIONAL) _____

PHARMACY LICENSE NUMBER(S) _____

I HEREBY CERTIFY THAT I HAVE TAKEN THIS TEST:

Signature/Date _____

(circle the correct answer)

1. Which influenza A virus subtype has been transferred from poultry to humans?
 - a. H5N1
 - b. H7N7
 - c. H9N2
 - d. All three subtypes (H5N1, H7N7, and H9N2) have been transmitted from poultry to humans
 - e. No virus subtype has been transmitted to humans yet
2. Outbreaks of avian influenza virus have _____
 - a. been confined to Africa
 - b. provided risks only to poultry
 - c. been responsive to amantadine
 - d. so far not had fatalities
 - e. been monitored by the WHO
3. Which of the following is **not true** about transmission of the influenza A virus (HPAI H5N1)?
 - a. Other animals can be intermediate vectors for transmission of this virus
 - b. Transmission can occur from direct exposure to infected bird droppings
 - c. Transmission can occur while handling or slaughtering infected birds
 - d. Direct transmission from human-to-human is common
 - e. Wild birds are a more common reservoir for transmission of this virus than domestic birds
4. Which one of the following statements is **true**:
 - a. Viruses very rarely mutate
 - b. There is no other possible vector than birds for transmission of the avian influenza A virus
 - c. Currently, human to human transmission of H5N1 is not likely
 - d. The H5N1 virus subtype can readily attach to RNA of any species
 - e. Avian influenza is currently a major source of infection in swine herds
5. Influenza A virus (H5N1) infections can be confirmed by any of the following **except**:
 - a. an elevated immunoglobulin A titer
 - b. a viral culture
 - c. a PCR assay for influenza A (H5N1) RNA
 - d. an immunofluorescence test for antigen of monoclonal antibody against H5
 - e. a four-fold increase in H5-specific antibody titer in paired serum samples
6. Common findings in patients that develop influenza A (H5N1) infections include all of the following **except**:
 - a. fever, cough, shortness of breath
 - b. shallow, decreased rate of respiration
 - c. pulmonary infiltrates on radiographs
 - d. lymphopenia, thrombocytopenia and increased aminotransferases in severe cases, respiratory and other organ failures
 - e. reverse transcriptase inhibitors
7. So far, which class of antiviral agents has shown the most usefulness in avian influenza A infections?
 - a. fusion inhibitors
 - b. general viral replication inhibitors
 - c. neuraminidase inhibitors
 - d. protease inhibitors
 - e. reverse transcriptase inhibitors

8. In addition to the antiviral medication, the mainstay of therapy is _____
 - a. oxygen and ventilation support
 - b. sympathomimetic bronchodilators
 - c. corticosteroids
 - d. respiratory stimulants including caffeine
 - e. gamma globulin
9. Vaccines for the prevention of avian influenza virus A (H5N1) are currently _____
 - a. available from Sanofi Pasteur
 - b. available from Chiron
 - c. available from the CDC
 - d. available from the NIAID
 - e. undergoing early trials
10. An individual who has been exposed to an infected bird or patient should be considered for prophylactic treatment with _____
 - a. amantadine 200 mg twice a day for 6 weeks
 - b. rimantadine 100 mg twice a day for 2 weeks
 - c. oseltamivir 75 mg once daily for 7-10 days
 - d. zanamivir 10 mg once daily for 4 weeks
 - e. ganciclovir 5 mg/kg twice a day for 7 days

Please Note: The CE processing fee has increased to \$7.50

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
Important to pharmacists	Agree		Disagree		
	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 Molecular Entities & Biologicals

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. 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. The FDA Approval Package 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 selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the *IDIS* database.

Therapeutic Potentials:

P = Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease.

S = Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs.

O = Orphan drug.

FDA Approvals

September – November 2005

Evidence of Safety and Efficacy

Deferasirox

*Exjade*TM Tablet for
susp, oral
Novartis
(1P, O)

Nisbet-Brown E, Olivieri NF, Giardina PJ, Grady RW, et al. Effectiveness and safety of ICL670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. *Lancet*. 2003; 361:1597-1602. (*IDIS* Article Number 497380)

Approved Nov. 2,
2005 for treatment of
chronic iron overload
due to blood
transfusions in adults
and children

A total of 24 patients were divided into three groups and were randomly selected to receive either once daily doses of 10, 20 or 40 mg/kg/day of deferasirox or placebo for 12 days in this trial that evaluated the short term safety, efficacy, pharmacokinetics and pharmacodynamics of the study drug. The investigators found deferasirox to be both safe and effective in the short term with a net iron excretion at 20 mg/kg/day equivalent to 0.3-0.5 mg iron/kg/day.

IDIS Search Terms [6 IDIS citations]

Deferasirox	64000006
Medical Care Compl-NEC	999.

Mecasermin

*Increlex*TM Injectable,
subcutaneous,
Tercica
(1P,O)

Guevara-Aguirre J, Vasconez O, Martinez V, Martinez AL, et al. A randomized, double blind, placebo-controlled trial on safety and efficacy of recombinant human insulin-like growth factor-I in children with growth hormone receptor deficiency. *J Clin Endocrinol Metab*. 1995; 80:1393-1398. (*IDIS* Article Number 350049)

Approved Aug. 30,
2005 for treatment of
growth failure in
children

This randomized trial included 17 pediatric patients who received either a 12-month course of rhIGF-I (mecasermin), 120 mcg/kg/day subcutaneously or 6 months of placebo followed by 6 months of study drug. The investigators found that the mecasermin group showed a significant and sustained increase in growth rate (from 2.9+/-0.6 to 8.6+/-0.4 cm/year). Though the study drug was found to be safe, the investigators recommended continuous and careful watchfulness for side effects.

IDIS Search Terms [7 IDIS citations]

Mecasermin	68200876
Dwarfism, Pituitary	253.3
Retardation, Physical	783.4

Nelarabine

*Aranon*TM Injection,
GlaxoSmithKline
(1P, O)

Berg SL, Blaney SM, Devidas M, Lampkin TA, et al. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the children's oncology group. *J Clin Oncol.* 2005; 23:3376-3382. (*IDIS* Article Number 536375)

Approved Oct. 28,
2005 for treatment of
T-cell acute
lymphoblastic
leukemia and T-cell
lymphoblastic
lymphoma.

This Phase II study included 121 patients under 21 years of age with refractory T-cell leukemia who were given nelarabine at doses of 1.2 g/m² daily for 5 consecutive days every 3 weeks, with dose reductions to 650 mg/m²/d and 400 mg/m²/d in cases of toxicity. In this study, nelarabine given as a single agent was found to be effective, showing a response rate of more than 50%, with neurotoxicity as the most notable side effect.

Kisor DF. Nelarabine: a nucleoside analog with efficacy in T-cell and other leukemias. *Ann Pharmacotherapy.* 2005; 39:1056-1063. (*IDIS* Article Number 536282)

An overview of the pharmacodynamics, chemistry and pharmacokinetics of nelarabine are provided in this review, as well as a summary of several clinical trials in both pediatric and adult patients. Information provided includes dosing, efficacy, and hematologic and neurologic toxicity.

IDIS Search Terms [8 IDIS citations]

Nelarabine	10060805
Leukemia, Lymphoid, Acute	204.0
NEOP, MGN-Lymph/Histio	202.0
NEC	

Nepafenac

*Nevanac*TM
ophthalmic susp,
Alcon
(1P)
Approved Aug 18,
2005 for treatment of
pain and
inflammation
associated with
cataract surgery.

The FDA approved **nepafenac** with a Priority Review classification. No published human studies have been found for entry into the *IDIS* database.

IDIS Search Terms [0 IDIS citations]

Pain NEC	780.91
Extraction, Lens	13.1
Aftercare NEC	V58.8

Ramelteon

*Rozerem*TM Tablet,
oral, Takeda Global
(1S)
Approved Jul 22,
2005 for treatment of
insomnia.

Nguyen NN, Yu SS, and Song JC. Ramelteon: A novel melatonin receptor agonist for the treatment of insomnia. *Formulary.* 2005; 40:146-155. (*IDIS* Article Number 535269)

The authors have provided an extensive review of the recently FDA approved insomnia medication, ramelteon, and have included information highlighting the novel mechanism of action, pharmacology, pharmacokinetics, safety and efficacy, drug interactions, a summary of clinical trials and an overview of the currently available therapies for insomnia.

IDIS Search Terms [1 IDIS citation]

Ramelteon	28240830
Disturbance, Sleep	780.5

Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the *IDIS* database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.



Goedken Completes Residency

Amber Goedken, Pharm.D., a 2004 graduate of the University of Iowa College of Pharmacy recently completed a 12 month Drug Information and Pharmaceutical Informatics residency at the Iowa Drug Information Network (IDIN). Her training provided opportunity to develop her skills in the routine provision of drug information services by being involved in answering questions from IDIN clients and supervising clerkship students involved at the center. She was able to provide assistance to a pharmacist in Nigeria who wanted to know

what was necessary to establish a functioning drug information center. She researched and then provided practical information on space needs, financial support, equipment and staffing needs to operate a center as well as providing a list of resources that are required to operate that center. *IDIS/Web* users can view her report in *IDIN Answers* by typing in “drug information center” and then looking under the category “other”.

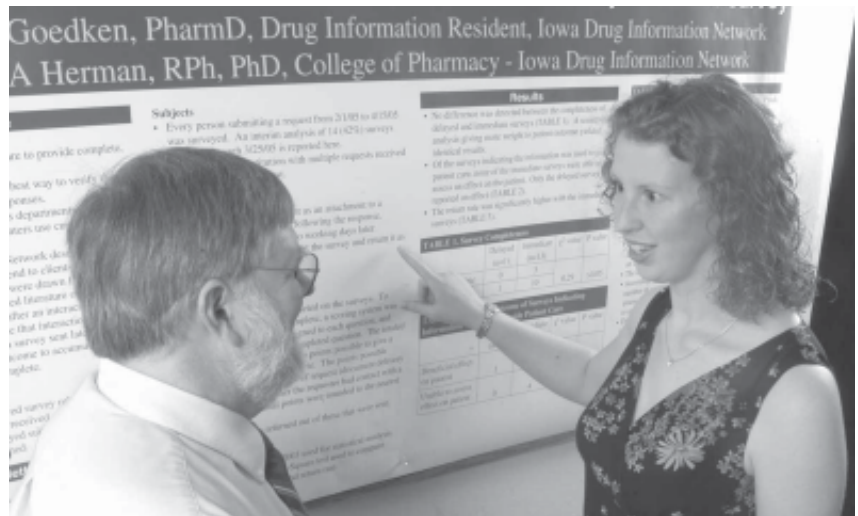
The residency gave Amber a chance to develop her research skills as she looked into the development of a quality assurance program to determine the impact of the drug information consultations being provided. She focused her work on determining the optimum time to survey clients on the impact of the information provided to them. She presented her project, “*Determination of the Preferred Time to Send a Quality Assurance Survey.*” at the Midwest Pharmacy Residents Conference, Omaha, NE, May 6, 2005.

Amber also had the opportunity to develop her writing and editorial skills as she was able to publish two papers, one here in the *World of Drug Information* and the other in *Annals of Pharmacotherapy*.^{1,2} She was involved in the editorial review process for several other articles also for the *World of Drug Information* and *Annals of Pharmacotherapy*. She was also afforded the opportunity to develop her teaching skills as she attended several training seminars and participated in the delivery of 10 invited talks or lectures. She was involved in the delivery of the Drug Literature Evaluation course as a teaching assistant. She was awarded a 2005 Wal-Mart Annual Conference Scholarship to attend the American Association of Colleges of Pharmacy Annual Meeting in Cincinnati. These opportunities had an impact on helping her decide that she would like to become a pharmacy educator. She is currently beginning a doctoral program in pharmaceutical socio-economics at the University of Iowa College of Pharmacy.

For more information on our residency program, please see <http://www.uiowa.edu/~idin>.

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2006

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Metformin and non-insulin dependent diabetes mellitus (NIDDM): when, if ever, are users at risk of developing lactic acidosis?

Background

Bailey¹ has detailed the history of biguanide use to treat diabetes from medieval times in Europe when *Galega officinalis* (goat's rue or French lilac) was a traditional therapy to 1957 when phenformin and metformin were introduced as glucose lowering agents for NIDDM. *Galega officinalis* was later found to be rich in guanidine. Before 1995, phenformin was the only available biguanide in the United States and was widely used in NIDDM patients in the 1960's and early 1970's. In 1976, phenformin was withdrawn from the United States market because of its association with lactic acidosis.² Metformin, although widely used in Europe, was not available in the United States until 1995 because of fear that metformin would also be associated with lactic acidosis.³ Public Citizen, a consumer advocacy group, issued a warning to the public, prior to the launch of metformin, "Do not use Glucophage."⁴ From May 1995 through June 30, 1996 the Food and Drug Administration (FDA) received 66 reports of lactic acidosis in diabetic patients treated with metformin. In 47 patients the diagnosis was confirmed with a lactate value of greater than 5 mmol/L. The FDA estimated the reported rate to be about 5 cases per 100,000 person-years. They noted that forty-three of the patients had at least one other risk factor for lactic acidosis.⁵

Published experience with metformin outside the United States reported the following cases of metformin associated lactic acidosis: in Sweden from 1987 through 1991, 2.4 cases per 100,000 patient-years.⁶ According to Brown and colleagues,⁷ previous reports from France, Sweden, and Switzerland described rates between 1 and 15 cases per 100,000 person-years. Stang and colleagues⁸ retrospectively examined data on over 22,000 patient years of exposure in Canada and reported an incidence rate of 9 cases per 100,000 person-years of metformin exposure.

The incidence of lactic acidosis associated with phenformin use in 1977 was estimated to be between 25 and 400 cases per 100,000 person-years; a rate many times higher than subsequent reports of metformin associated lactic acidosis.⁹ Cohen and Woods¹⁰ in a recent review concluded that phenformin is about 10 times as likely as metformin to induce lactic acidosis. They estimated the absolute risk of metformin associated lactic acidosis to be between 5 and 14 cases per 100,000 patient-years.

Lactic Acidosis

Interested readers are referred to reviews by: Cohen and Woods¹⁰, Oliva¹¹, Kreisberg¹² and Mizock¹³ for detailed discussion of the biochemistry, clinical features and therapy of lactic acidosis.

There are several fundamental unresolved issues that complicate any discussion of biguanides and lactic acidosis. First, the majority of diabetic patients have several predisposing conditions for hypoxia including microvascular and macrovascular disease, and decreased hemoglobin function. In the majority of reported cases of biguanide associated lactic acidosis there was at least one other condition that predisposed them to lactic acidosis. Besides the presence of a biguanide, other important factors that may contribute to lactic acidosis include: acute alcoholism, acute infections, liver disease, and renal insufficiency even if mild or transient.¹⁶ In their discussion of the natural history and course of acquired lactic acidosis in adults, Stackpole and colleagues¹⁵ reminded us, that in most cases when lactic acidosis is diagnosed both hypoxic and non-hypoxic causes are present. In their opinion, pure type A or type B lactic acidosis rarely exists.

Second, the incidence of so called "idiopathic lactic acidosis" in patients with diabetes mellitus before biguanides were available is controversial. Oliva¹⁰ asserts that lactate levels are usually normal in untreated diabetics. He considers most cases of lactic acidosis in diabetic patients to be caused by shock from numerous causes. According to Kreisberg¹², even if almost 50% of the reported cases of idiopathic lactic acidosis have occurred in diabetic patients, an association between the two conditions has not been proven. He states: "idiopathic lactic acidosis has become virtually nonexistent since the removal of phenformin from the market...". On the other hand, one recent editorial has stated: "diabetes alone is an equally relevant, if not more relevant, risk factor for lactic acidosis than is metformin use."¹⁴

Third, during the early period of development of lactic acidosis, not associated with circulatory shock, Stackpole and colleagues¹⁵ and Cohen¹⁶ agree that: the blood pressure may be well maintained and the extremities can be warm and well perfused. If the condition, however, is not promptly treated or does not respond to treatment, they warn shock will develop within a few hours.

Biguanide treated diabetics – clinical features of lactic acidosis

Luft and colleagues¹⁷ reviewed 330 diabetic patients who developed lactic acidosis after being treated with a biguanide, 50% of whom died. The primary reason we must be so vigilant whenever lactic acidosis is a possibility is the very high death rate of 50 % within hours or a few days associated with this

adverse effect. From 195 patients, the following symptoms were reported by Luft and colleagues¹⁷ before the diagnosis of lactic acidosis: vomiting 100; somnolence 98; nausea 71; epigastric pain 69; anorexia 52; hyperpnea 50, lethargy 29, diarrhea 27, thirst 8. At the time of diagnosis, dehydration was apparent in 62 cases, skin pallor in 62 cases and cyanosis in 27 cases. Of the 143 patients whose medical history was known, 44% had cardiovascular disease, 35% had renal disease, 25% infections, 19% pulmonary disease, 15% liver disease, 24% shock (in only 13% as 1st sign) and 17% anuria. Seventeen patients were alcoholics or had taken large amounts of alcohol acutely. The respiratory rate varied with the severity of the metabolic acidosis. The respiratory rate was over 20 per minute in 94 cases with a Kussmaul type in 70 cases. The laboratory data indicated a decompensated metabolic acidosis with the expected ventilatory response. Many phenformin treated patients had normal or near normal serum creatinine levels at the time of diagnosis of lactic acidosis. Metformin associated lactic acidosis occurred only with marked renal impairment; the lowest serum creatinine was 3.0 mg/dl. They concluded that biguanide associated lactic acidosis occurred rarely in the presence of normal renal function.

Reports of metformin associated lactic acidosis in patients who may have had contraindications

Calabrese and colleagues¹⁸ identified 204 hospitalized patients who received metformin. Of the 204 patients, 126 had either an absolute or relative contraindication to metformin use. The most frequent absolute contraindication reported was an elevated serum creatinine (> 1.5mg/dl in males or 1.4 mg/dl in females), that occurred in 32 instances. The most frequent relative contraindication was the concomitant use of a cationic drug, that occurred in 97 instances. In two patients who died and one who survived, high lactate concentrations (>7 mmol/L) were present. All three patients had renal disease and there was a temporal relationship between their metformin administration and their elevated lactate levels. Metformin associated lactic acidosis (MALA) could not be ruled out in any of the cases. There was no mention of the diagnosis of lactic acidosis or metformin associated lactic acidosis in any of them. They acknowledge that metformin has been shown to increase intestinal lactate production when the patient is hypoxic or experiences the decreased lactate elimination that may be associated with hepatic or renal failure. Calabrese and colleagues¹⁸ assert that “it

remains unclear whether metformin is a contributing cause of lactic acidosis or if it is merely a drug with a coincidental link to lactic acidosis.” They are concerned the failure to follow metformin’s prescribing guidelines might result in unacceptably high rates of MALA, and lead to the drug’s removal from the market as was the case for cisapride and several other compounds that were used in contraindicated settings.

Sulkin and associates¹⁹ examined the records of 89 patients attending a university based diabetes clinic over a three month period and found that over fifty percent of the patients had concomitant illness or other issues listed as relative or absolute contraindications to metformin use. Two patients had elevated serum creatinine levels, two others evidence of cardiac failure, and two more had chronic hepatic disease; each a potential cause of hyperlactemia. They were particularly concerned with clear evidence of chronic renal impairment in two patients, a well known cause of metformin accumulation. They note the only case of fatal MALA on their service during the past decade was in a patient thought to have a low risk profile.

McCormick and colleagues¹⁴ reported the summary of German experience in 308 metformin patients, of whom 73% had at least one contraindication, with no cases of MALA. They also reported a study from Scotland of 1847 metformin patients in whom 24.5% had at least one contraindication. Only one case of lactic acidosis due to cardiac failure was reported in the group from Scotland. They believe the absence of lactic acidosis in metformin patients with contraindications over the last decade supports their call to eliminate many of the current contraindications.

Evidence of metformin accumulation in MALA

Lalau, a French endocrinologist, and colleagues^{20,21,22} have published a series of articles investigating the role of metformin accumulation in MALA. The first paper measured lactate levels in 14 patients who had lactic acidosis (pH < 7.35 and lactate concentration > 5 mmol/L) while on chronic metformin therapy.²⁰ Ten of the patients had metformin accumulation (plasma metformin levels 4.1-84.9 mg/l, normal value 0.6 +/- 0.5mg/l) because of failure to discontinue metformin in the presence of other conditions affecting its renal clearance (serum creatinine concentrations ranging from 3.04 to 12.34 mg/dl). The remaining four patients with less severe renal disease (serum creatinine concentrations ranging from 1.58 to 3.94 mg/dl) experienced no metformin accumulation (plasma metformin levels 0.03-0.7 mg/l). Hospital mortality was low in the 10 patients with metformin accumulation, and was not

related to the metformin plasma level. The three patients who died from the group of ten had end-stage hepatic or cardiac failure. They insist that if MALA is a type B lactic acidosis, as biguanide associated lactic acidosis has been assumed to be, there should be no other pathologic condition present in addition to the metformin accumulation.

Next, his group used discharge and laboratory data from over 41,000 Kaiser Permanente NIDDM patients from Oregon, Georgia and Hawaii from the time period before metformin was available in the United States.²¹ They found, four confirmed, three possible, and three borderline cases of lactic acidosis. In each case there was at least one severe medical condition that could have caused the acidosis. His group believes that the majority of cases of MALA have occurred in the individuals who were acutely ill with other conditions that could have been the cause of the acidosis. They believe that if metformin accumulation causes or worsens lactic acidosis the rate should be greater in the treated group. Their finding of a similar rate of lactic acidosis in NIDDM patients before metformin was available is against metformin accumulation as a cause of lactic acidosis. They then searched the worldwide published literature for English and non-English language published reports of so called MALA from May 1995 through January 2000. Reports associated with metformin overdose or contrast media associated renal failure were excluded.²² They found reports describing 22 patients with lactic acidosis (lactate > 5 mmol/l, pH < 7.35). In only four patients was the metformin concentration available, one of whom had no accumulation. In the 18 remaining patients primary renal failure was likely or confirmed in 14, absent or unlikely in 6 and uncertain in 2. In the 12 patients in which lactic acidosis occurred without other clinically evident pathology, death occurred once and was related to the refusal to undergo dialysis therapy. They pointed out that in the absence of metformin level data, increased serum creatinine levels that have almost always been associated with metformin accumulation may be useful. But a serum creatinine level does not substitute for an adequate history of renal function. Metformin accumulation requires both impaired metformin elimination and continuation of metformin. High serum creatinine levels in metformin treated patients are not therefore necessarily associated with metformin accumulation. In each case a determination of whether or not the renal failure is primary or

secondary to the illness precipitating the lactic acidosis is critical. Only then can it be estimated whether or not the renal function has been decreased long enough to be associated with metformin accumulation. They concluded that the term MALA is confusing as it relates to pathophysiology and prognosis. They have found a high mortality rate in metformin unrelated lactic acidosis and no evidence of mortality in cases where metformin accumulation exists in isolation. They do not believe the case has been made to blame metformin accumulation, associated with therapeutic use, for lactic acidosis.

Stades and colleagues²³ in Holland also conducted a literature based review of reports of MALA from 1959-1999. They reviewed 47 cases with (lactate concentrations > 5 mmol/l and pH < 7.35). They concluded that the belief there is a simple relationship between therapeutic metformin use in NIDDM patients and lactic acidosis was not confirmed by the cases they reviewed.

Recent editorials on metformin's contraindications

A pair of editorials very recently published in *Canadian Medical Association Journal* has called for elimination of many of the metformin contraindications¹⁴ or keeping them for the time being.²⁵

McCormick and colleagues¹⁴ consider the absence of reports of lactic acidosis in the various groups of patients who "had contraindications" a sort of evidence that metformin probably does not cause or contribute to lactic acidosis. They also list as one of their key points "even in patients with contraindications the benefits of metformin in NIDDM patients clearly outweigh any potential risks."

Fantus²⁴ concurs that metformin offers significant benefits for some patients, and cites the United Kingdom Prospective Diabetes Study (UKPDS), that found advantages for newly diagnosed obese NIDDM patients who received metformin when compared with diet or a sulfonylurea. The metformin treated patients had a 7% reduction in diabetes related deaths and a 10% reduction in total mortality after 10 years of follow-up. However, he cautions that the benefits of metformin compared to other therapies was not based on a population with contraindications to the drug, and these benefits can not necessarily be extrapolated to the different risk group. He also cautions that the retrospective and observational data which have not found a high rate of lactic acidosis in patients taking metformin can not be interpreted to imply

safety in the subpopulation with contraindications. He maintains that the contraindications to metformin of renal impairment, congestive heart failure, severe liver disease, or age greater than or equal to 80 years should continue to be observed. He notes that there are pharmacologic and pharmacokinetic reasons that metformin is much safer than phenformin, in particular that metformin does not require hepatic metabolism and is excreted unchanged by the kidney. Nonetheless, he does not recommend changes in the guidelines for the use of metformin.

Recent case of MALA in a typical NIDDM patient without contraindications

A recent case report by Mallick²⁸ describing possible metformin induced acute pancreatitis casually notes: "renal failure precipitated the metformin toxicity." The patient was a 61 year-old female with a prior medical history of NIDDM, myocardial infarction, and ischemic heart disease. Her renal function had been checked one month earlier and was normal. Medications included: aspirin, atenolol, clopidogrel, amlodipine, lisinopril, nitrate, metformin, nateglinide and ibuprofen. She had a four day history of vomiting and one day history of abdominal pain prior to admission. Laboratory data on admission included: lactate 25 mmol/l, pH 7.0, anion gap 43 mmol/l, BUN 80, serum creatinine 5.8. Her blood pressure dropped to 65/50 mmHg with a urine output of 5ml/hour. She was transferred to intensive care and hemodialyzed. Her lactic acidosis resolved after hemodialysis. The combination of ibuprofen and lisinopril was thought to have caused acute renal failure that reduced metformin excretion with resulting severe lactic acidosis and pancreatitis.

There seem to be no obvious contraindications to metformin use in this case, unless there is a cationic drug. The focus of this case could have been the occurrence of MALA in a patient without prior existing contraindications to metformin.

Summary

Almost 25 years ago Dr. Cohen, a British expert in this area, when writing on phenformin and lactic acidosis made the following observations:¹⁶ "... although the number of reported cases is likely to represent the tip of the iceberg, the condition is probably not very common in absolute terms amongst patients receiving

phenformin; (even less common it would appear with metformin), there is no means of assessing the true incidence. But, unlike most adverse effects, lactic acidosis has a very high mortality." "Renal failure is not always very severe, and a review of the literature suggests that lactic acidosis is likely to arise in a diabetic on phenformin when for some reason there is a mild, potentially reversible deterioration in renal function due to administration of diuretics, or to urinary tract infection (UTI), heart failure, trauma (surgical), or progression of diabetic glomerulosclerosis; accumulation of phenformin to a critical level results and this precipitates lactic acidosis. It should be noted that renal failure itself, is not a recognized cause of lactic acidosis."

We can hope the past experience that suggests metformin is at least 10 times less likely than phenformin to cause lactic acidosis will prove accurate. In heart failure patients today, unless contraindicated, they will be on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker with their well known pre-renal effects. For the past twenty or thirty years it has been clear that typical exacerbations of heart failure or chronic obstructive pulmonary disease or both can cause hypoxic hepatitis with a shock state occurring in only about 50% of cases except toxic/septic shock.²⁵ It may be that such typical exacerbations of heart failure or chronic obstructive pulmonary disease can cause a hypoxic form of renal failure or localized hypoxic states leading to lactic acidosis. In any event, until we have better information, my vote would be to continue metformin's current contraindications with careful attention to any pre-renal insult or use of other cationic drugs that could block the renal tubular secretion of metformin that accounts for the majority of its renal clearance.²⁶ Any metformin user who experiences mild acute or chronic renal failure is at risk for developing lactic acidosis. In such a setting it would be prudent to hold metformin until renal function has returned to baseline.

EDITOR'S 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 ARTICLE ILLUSTRATES IDIS DATABASE USE CONTRIBUTING DIRECTLY TO PATIENT CARE OUTCOMES. THE RESPONSIBILITY FOR ERRORS IS THE AUTHOR'S ALONE. THE ARTICLE DOES NOT NECESSARILY REPRESENT HOSPITAL VIEWS AND RECOMMENDATIONS. WE HOPE YOU FIND THE INFORMATION INTERESTING AND USEFUL. WE WELCOME COMMENTS. IF YOU ARE INTERESTED IN SHARING YOUR EXPERIENCES USING THE IDIS DATABASE, PLEASE CONTACT DONNA-BRUS@UIOWA.EDU

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World of Drug Information is published quarterly

(March, June, September, December) by the Division

of Drug Information Service.

Editor-in-Chief Dr. Kevin Moores

Editor Donna Brus

Production/Design Coordinator Julie Tomash

Photographer David Luck

ISSN# 1529-4331

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