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CURRENT CLINICAL ISSUES

Smallpox: The next threat?

Introduction

The few cases of anthrax that occurred in the U.S. last fall were tragic, unnerving, and costly but nothing in comparison to “what could have been” if those same few cases of anthrax had been smallpox. Smallpox is a particularly menacing disease that is transmissible from person to person, has a 30% death rate, and leaves surviving victims horribly scarred with pox marks.

On December 9, 1979 the World

Health Organization certified that the disease smallpox had been eradicated. The variola virus that causes smallpox, however, has not been eradicated from earth. In a December 31, 2001 CDC Webcast, Department of Health and Human Services Secretary Tommy Thompson reported that both the United States and Russia maintain stockpiles of the smallpox virus. He also reported that they have anecdotal evidence that some of the smallpox virus may have been taken from the Russian facility and countries such as Iraq and North Korea may have the virus. The threat of a bioterrorist attack involving smallpox is of enough concern that the Department of Health and Human Services established a contract to have enough smallpox vaccine on hand for every U.S. citizen by the end of 2002. There is no plan to vaccinate the population without evidence of an attack as the smallpox vaccine is not without potentially serious side effects. As with anthrax, the key to minimizing the consequences of the disease is early detection and rapid response.

Smallpox

Smallpox is an acute infectious disease caused by the variola virus. There are two forms of the

disease, variola major and variola minor. Variola major is the more severe form of the disease with a 20-50% fatality rate. (Neff) Person-to-person transmission is the most common mode of transmitting the disease. Typically, symptoms of smallpox begin 12-14 days (range: 7-17) after exposure. (Fenner) The initial symptoms are a 2-3 day prodrome of high fever, malaise and prostration with severe headache and backache. This stage is followed by the appearance of a maculopapular rash that progresses to papules 1-2 days after the rash appears. The oral mucosa, face and forearms are the sites where the rash appears first and then spreads to the trunk and legs. Vesicles appear on the fourth or fifth day after the appearance of rash and pustules appear by the seventh day (CDC, June 22, 2001) (images at <http://www.bt.cdc.gov/Agent/Smallpox/SmallpoxImages.asp>). Scab lesions occur around the fourteenth day. People infected with variola virus are not infective during the prodromal period. (Rotz) They become contagious when the first lesions appear and remain contagious until the last scab falls off. Previously vaccinated persons show a

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modified course of smallpox. (Atkinson) The prodromal period still occurs but is less severe. The skin lesions tend to evolve more quickly, are more superficial, and may not show the uniform characteristic of more typical smallpox. Modified smallpox is rarely if ever fatal.

Diagnosing

The three major diagnostic determinants of smallpox are: 1) a prodrome fever of at least 101°F with either prostration, headache, backache, chills, vomiting or abdominal pain, 2) rash lesions are deep in the skin, firm or hard to the touch and well circumscribed, 3) all lesions are in the same stage of development on all areas of the body. (Galil) The five minor diagnostic criteria of smallpox are: concentration of lesions on face and extremities with sparing of the trunk, the rash first appears in the mouth, face or forearms, the patient is toxic or moribund, lesions progress slowly from papules to pustules, and lesions appear on palms and soles of feet. (Galil) Varicella infection or chickenpox typically does not exhibit the high prodromal temperature seen in smallpox. (Galil) Varicella lesions are raised, fluid filled and delicate in appearance, whereas smallpox lesions are embedded in the skin and are firm or hard to the touch. Varicella lesions are also more predominant on the trunk and back unlike smallpox lesions that appear more frequently on the extremities and face. (Galil)

Prevention

There are currently no approved drug treatments for smallpox. In the 1960s, methisazone was licensed for prophylaxis of smallpox. (Franz) Due to its controversial efficacy and gastrointestinal side effects it is no longer available. Researchers are hopeful that some of the new antivirals may be efficacious in treating or preventing smallpox. Cidofovir has shown promising results in protecting mice exposed to cowpox virus. (LeDuc) Other drugs that have shown promising in vitro results include adefovir dipivoxil, cyclic cidofovir and ribavirin. (Franz)

All currently available smallpox vaccines are comprised of live virus preparations of infectious vaccinia virus. No vaccine contains the variola

virus. Neutralizing antibodies induced by vaccinia vaccine are cross protective for other Orthopox viruses, such as monkeypox, cowpox, and variola viruses. (CDC, June 22, 2001) The vaccine is administered with a bifurcated needle with 15 rapid, vigorous punctures of the skin over the deltoid

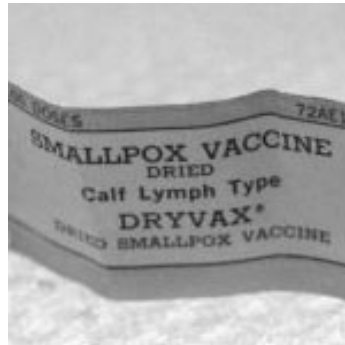
muscle or the posterior aspect of the arm over the triceps muscle. One droplet of the vaccine contains the recommended dose of vaccine. (Henderson) To verify that the vaccine was effective in producing a protective immune response, the vaccination site should be inspected 6-8 days after vaccination. A major reaction confirms successful vaccination (CDC, June 22, 2001) (images at <http://www.bt.cdc.gov/Agent/Smallpox/VaccineImages.asp>).

A major reaction is defined as “a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer.” (CDC, June 22, 2001) Typically, the inoculation site becomes reddened and pruritic 3-4 days following vaccination. This becomes umbilicated and pustular by days 7-11 after vaccination. This pustule then becomes crusted, forming a scab which falls off by the end of the third week leaving a permanent scar. For persons that have been previously vaccinated, the reaction may not be as pronounced. Revaccination in previously vaccinated persons, is considered successful if “a pustular lesion is present or an area of definite induration or congestion surrounding a central lesion (i.e., scab or ulcer) is visible upon examination 6-8 days after revaccination.” (CDC, June 22, 2001)

Anything less than a major reaction is considered an “equivocal reaction” and revaccination is necessary. Reasons for an equivocal response include immunity to smallpox, impotent vaccine, or incorrect administration of vaccine. If after using another vial or vaccine lot the revaccination still fails to produce a major reaction, the CDC or the state or local health department should be consulted before giving a third dose. (CDC, June 22, 2001)

Immunity

Many people who received the smallpox vaccine as a child may erroneously believe that they are still immune to smallpox. It is thought that substantial protection against smallpox exists for up to 5 years after primary vaccination and substantial but waning immunity may persist for 10 years or more. (Atkinson) Revaccination every three years would



be necessary to assure immunity. (Neff, CDC June 22, 2001) In the U.S., routine vaccination for smallpox ended in 1972. Since it has been at least 30 years since most people were vaccinated, it is assumed that the majority of the population would be susceptible to infection (Henderson). Persons that were previously vaccinated may, however, show an accelerated immune response to the vaccine compared to those receiving the vaccine for the first time. (CDC, June 22, 2001) Administration of the vaccine within a few days of exposure can prevent or decrease the severity of the disease. (Atkinson)

Side Effects

Commonly occurring side effects of the vaccinia vaccine are scarring, fever, and autoinoculation. A papule forms at the site of inoculation which becomes vesicular and then pustular. The pustule dries forming a scab which leaves a scar when it eventually falls off. Fever greater than 100°F is also often seen in 70% of children after primary vaccination. Thirty-five percent of children have fever greater than 100°F after revaccination. (CDC June 22, 2001) The primary site of vaccination continues to shed vaccinia virus until the scab falls off. The virus from this site may be spread by touching it and then touching other areas such as the face, eyes, mouth, genitals or rectum resulting in autoinoculation.

(<http://www.bt.cdc.gov/Agent/Smallpox/VaccineImages.asp>). Other more severe adverse reactions to the smallpox vaccine include eczema vaccinatum, generalized vaccinia, progressive vaccinia, postvaccinial encephalitis and vaccinial keratitis. (Henderson, CDC June 22, 2001) A recent study of Israeli army recruits, reported an overall complication rate of 0.4 per 10,000 vaccinees. The most frequent complications were eczema vaccinatum (0.15 per 10,000) and generalized vaccinia (0.09 per 10,000). (Haim) The incidence and severity of side effects is greater in those receiving the vaccine for the first time than in those being revaccinated. Contraindications for nonemergency vaccine use include: history or presence of eczema, other acute, chronic or exfoliative skin conditions, immunosuppression,

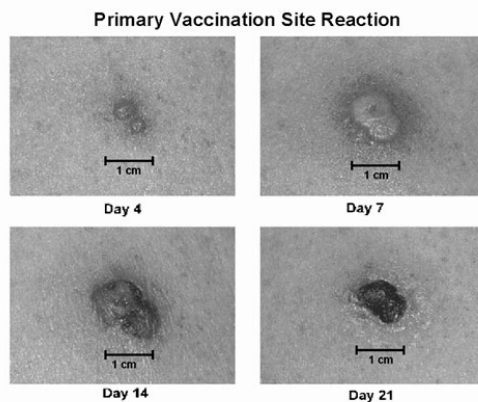
pregnancy, age < 18 years or vaccine component allergy. If persons are exposed to smallpox virus there are no contraindications to administering vaccine. (CDC, June 22, 2001) If there is a smallpox emergency, but no virus exposure, the contraindications are the same as for a nonemergency setting. Depending upon the severity of the adverse reaction, vaccinia immunoglobulin may be used to treat cases of vaccine complications.

Conclusion

By the time most people are considered contagious, they are so sick that they are home in bed. Therefore most secondary infections occur in family members or caregivers (Henderson). Once identified, the disease may be contained by isolating the patients and vaccinating those in direct contact with the patients. Early administration of the vaccine is also effective in decreasing the severity of the disease. (Atkinson) The smallpox vaccine is relatively safe and effective but is not devoid of bothersome to severe adverse reactions. For these reasons the Department of Health and Human Services and the

Centers for Disease Control and Prevention do not see the need to preemptively vaccinate the entire nation until an outbreak is identified. (Koplan) Because of the highly mobile population, an outbreak anywhere in the world could have worldwide impact. Having enough vaccine on hand to treat the entire population is

necessary. Hopefully, the need to vaccinate the population against smallpox will not arise. The key elements to being prepared for a smallpox outbreak are "...surveillance and diagnosis to achieve early detection of an introduced case; isolation of the case or cases; and identification and vaccination of the contacts of the case or cases." (Koplan) Pharmacists and other healthcare professionals can aid in this preparedness by remaining informed and up-to-date about the smallpox disease, the vaccination and its side effects.



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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 020-000-02-015-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, 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 September 1, 2003 to receive credit.

Assessment Questions

Circle the most appropriate answer

1. The vaccine used to prevent smallpox is comprised of:
 - a. variola minor
 - b. variola major
 - c. vaccinia virus
 - d. monkeypox virus
2. Patients who have contracted smallpox are contagious:
 - a. when the first lesions appear
 - b. until scabs form
 - c. until all scabs fall off
 - d. a and c
3. Typically, symptoms of smallpox infection occur ____ days after infective exposure:
 - a. 1-2
 - b. 3-4
 - c. 5-7
 - d. 12-14
4. Which of the following drugs has shown in vitro efficacy against variola virus?
 - a. ritonavir
 - b. saquinavir
 - c. cyclic cidofovir
 - d. amantadine
5. Which of the following symptoms are indicative of smallpox:
 - a. lesions on the soles and palms
 - b. lesions are raised, fluid filled and delicate in appearance
 - c. lesions are more predominant on the trunk and back
 - d. low grade fever
6. Contraindications to smallpox vaccination in a nonemergency setting include all of the following except:
 - a. < 18 years of age
 - b. pregnancy
 - c. immunosuppression
 - d. vaccination against smallpox within the last 3 to 5 years
7. A "major reaction" confirms _____.:
 - a. allergy to the vaccine
 - b. unsuccessful vaccination
 - c. successful vaccination
 - d. previous inoculation
8. Fever of at least 100° F has been reported in ____ of children receiving the smallpox vaccine for the first time.
 - a. 70%
 - b. 50%
 - c. 30%
 - d. 10%
9. To verify that vaccination was successful, the site of vaccination should be examined _____ days after vaccination.
 - a. 1-3
 - b. 3-5
 - c. 4-6
 - d. 6-8
10. A person is considered immune to smallpox infection if:
 - a. they have been vaccinated at any time in their life.
 - b. they received the vaccine within the last 3 years and exhibited a major reaction.
 - c. they received the vaccine no more than 10 years ago.
 - d. they are at least 27 years of age and received the smallpox vaccine as a child.

Directions

Select the most appropriate answer for each of the following questions and circle the corresponding letter on the answer sheet.

To receive one hour of continuing education credit (0.1 CEU) for successful completion of this program, you must:

1. Complete the answer sheet.
2. Print or type your name, address, social security number and pharmacy license number(s) in the space provided on the CE registration form.
3. Complete the program evaluation.

Mail a \$5.00 check made out to the College of Pharmacy, your completed answer sheet/registration form/evaluation to:

**Division of Drug Information Service
ATTN: Donna Brus
The University of Iowa
100 Oakdale Campus N330 OH
Iowa City, IA 52242-5000**

Certificates will be issued to those who score 70% or higher. Those who score below 70% will be notified, and no credit will be recorded. Allow four weeks for processing.

ANSWER SHEET

- | | | | | | | | | | |
|----|---|---|---|---|-----|---|---|---|---|
| 1. | a | b | c | d | 6. | a | b | c | d |
| 2. | a | b | c | d | 7. | a | b | c | d |
| 3. | a | b | c | d | 8. | a | b | c | d |
| 4. | a | b | c | d | 9. | a | b | c | d |
| 5. | a | b | c | d | 10. | a | b | c | d |

CE REGISTRATION

(please print)

ACPE Program #020-000-02-015-H01

Title of Educational Activity (Article) Smallpox: The next threat?

Name _____

Address _____

City _____ State _____ Zip _____

Social Security Number * _____

Pharmacy License Number(s)* _____

*The University of Iowa College of Pharmacy requests this information for the purpose of processing your registration. No persons outside The University of Iowa College of Pharmacy are routinely provided this information.

I hereby certify that I have taken this test:

Signature Date

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.

IDIS/Web Search Tips

SEARCH TIPS

The start of a new year brings many new users to *IDIS/Web*. What is the most efficient method of selecting terms for a search? In many cases direct searches of the Drug, Disease, Descriptor and/or Journal Fields with a valid term could be the best choice. If you are not sure which valid term you need to use, the Look Up option is available for the Drug, Disease, Descriptor and Journal fields on the Advanced Search template.

The Drug, the Disease and the Journal Look Up pages have a search field. Terms submitted in this field will retrieve all valid terms that contain the term entered. If truncation is used in the search field, the truncated form should be enclosed in quotation marks. For instance, entering “*furos**” in the Drug Look Up search field retrieves the valid terms **FUROSEMIDE** and **FUROSEMIDE, BUTOXYMETHYLEN**. This same principle applies to the Disease and the Journal Look Up searches. To place a term in the search template, simply highlight the term and click. The Journal Look Up page also offers an All Journals option. Choosing this will present a list of all journals indexed.

Choices are made from this list by checking the adjoining box and submitting. This journal list also gives the valid *IDIS* abbreviations, journal title changes and years the journal has been indexed.

The Descriptor Look Up option page offers a list of all *IDIS* valid descriptor terms. Select the desired descriptors by checking the adjoining box and submitting. Note that the default Boolean term for this list is ‘AND’, but ‘OR’ can be selected when needed.

These Look Up options are especially useful when the searcher does not know, and would like to use, the valid *IDIS* term. For the Descriptor and Journal fields, the Look Up also provides a list of all available terms. Familiarity with the search options makes searching *IDIS/Web* faster, easier and more efficient.



Nicola Sarrazin, R.Ph., Pharm.D.

Perspective from an *IDIS* Subscriber



Re: Probable metoclopramide associated parkinsonism, incontinence, and dysphagia masquerading as multiple system atrophy, weight loss, and major depressive disorder.

DATA:

VITALS – BLOOD PRESSURE 110/60; PULSE 112; RESPIRATORY RATE 22; TEMPERATURE 98.2 on admission; ALLERGY –none; 84 Year-old White Male; 67 inches/139 lbs; CALCULATED CREATININE CLEARANCE value of 42 mL/min (11/21); LIVER FUNCTION TESTS - within normal limits expect ALKALINE PHOSPHATASE 672 U/L; THYROID STIMULATING HORMONE 2.12 uIU/ml; VITAMIN B₁₂ >1500pg/ml; FOLIC ACID 11.2 ng/ml.

MEDICATIONS:

(On admission to Hospice) - levothyroxine 0.1 mg qd, metoclopramide (MET) 10mg qid, levodopa/carbidopa SR 25/100 bid, bupropion SR dose unknown, dronabinol dose unknown. (On discharge) - levothyroxine 0.1 mg qd, mirtazapine 15 mg hs, miconazole 2% cream qd, acetaminophen 650mg q4hprn, levodopa, carbidopa 25/100 finish tapering regimen (twice a day for seven days, then at bedtime for seven days, then discontinue).

HISTORY OF PRESENT ILLNESS:

The patient was scheduled into our Hospice Clinic on 11/15/01 after his private medical doctor insisted that he was dying and needed placement, although there was no cancer or other terminal illness diagnosed. He had deteriorated functionally over the past year after having a very active life. There were two recent hospitalizations (at other institutions), the first with cough, shortness of breath and a twenty pound unintentional weight loss (04/03/01-4/06/01) and the second with a chief complaint of progressive dysphagia with solid and liquid foods (6/05/01-6/11/01). The major new diagnosis for the first admission was pneumonia and for the second was iron deficiency anemia. The patient had seen a gastroenterologist (date uncertain) in the past who prescribed MET 10mg for an intermittent syndrome of abdominal pain and bloating. Within a few weeks the patient noticed the sub acute onset of new slowness initiating movement, bilateral stiffness, and reduced activity level. He was seen by a neurologist, a few months after seeing the gastroenterologist, who diagnosed multiple system atrophy and started Sinemet™ therapy. The patient began to experience depression in early 2001 after his medical difficulties occurred.

During the two months prior to Hospice admission, the patient had continued weight loss, a percutaneous enterogastric (PEG) tube placement, several “falls,” some confusion, and continued urinary incontinence. He was believed to be noncompliant with medications and feedings. His son stated that his father was suffering from “severe depression” with suicidal ideation, irritability, and psychomotor retardation. During the same time period the patient’s wife, who has Alzheimer’s dementia,

became more forgetful, repetitive, and aggressive. He was seen by liaison psychiatry whose diagnostic impression was severe major depression, single episode with multiple system atrophy and deconditioning.

PRIOR MEDICAL HISTORY:

Post-traumatic stress disorder, hypothyroidism (status post thyroidectomy), multiple system atrophy, deconditioning, benign prostatic hypertrophy (status post TURP 1994), diverticulosis + possible multiinfarct cerebral disease, sleep apnea.

HOSPITAL COURSE:

The patient’s condition worsened during his five day stay in the Hospice unit. He was very quiet, and did not speak unless spoken to. He slept most of the day and did not wish to be out of bed for any length of time. He required assistance with all transfers. He had an episode of vomiting with possible aspiration pneumonia, which was treated with IV antibiotics. His sodium was 129 mmol/L. A modified barium swallow was done and was not consistent with dysphagia. He was transferred to the Geriatric Evaluation & Management (GEM) team for further evaluation.

On examination, the patient was noted to have masked facies, hypophonia, mild bradykinesia, mild rigidity, a slightly stooped posture, and instability on turning. There was no tremor or cogwheeling. He could get up and out of bed without assistance and walked only with hands on assistance. His prior neurological diagnosis was reevaluated in light of the fact that the neurological syndrome emerged only after MET was begun. The plan

was to discontinue MET, and levodopa/carbidopa, start on oral feedings plus nighttime tube feedings, and begin rehabilitation therapy. He received his last dose of MET at 1:00pm on 11/28/01.

The patient was referred to Physical Therapy but missed his appointments on 11/21/01 and 11/23/01. When seen on 11/24/01 he did not initiate conversation and his motivation was poor. When seen on 12/07/01 he would initiate conversation and his motivation was much improved. By 1/23/02 he had attended 34 sessions for general strengthening exercises and had progressed from needing standby assistance to independent ambulation with a walker with wheels for 200 feet or with a cane for 200 feet. His motivation had changed from not wanting to do anything to becoming an active participant in physical and recreational therapy. He demonstrated good motivation and participation in his program and fully met all goals. The plan was to discharge him to home with the belief he should do well in his return to independent living.

Within two weeks of discontinuing his MET, the

patient's mood and strength had improved and he was no longer incontinent of urine. He continued to improve clinically until he was ready for discharge. At the time of discharge his parkinsonian syndrome had almost completely resolved, his gait and balance were improved, he was no longer depressed, and was eating a normal diet without any difficulty.

LITERATURE:

Background

Local anesthetics of the procaine type were known to have a mild antiemetic effect. Alteration of the procainamide molecule lead to more powerful antiemetic substances. French workers were fascinated because this series of compounds were devoid of depressant effects on the central and autonomic nervous systems. Their work led to the rediscovery of MET which had been synthesized earlier in Belgium. MET inhibited apomorphine associated vomiting with the virtual absence of CNS depression. It has now been established that the antiemetic action of MET is due to blockade of dopaminergic receptors in the chemoreceptor trigger zone. (Schulze-Delrieu, 1979, Schulze-Delrieu, 1981)

(Reglan™) MET has been available in the United States since 1979, however it was introduced into practice in France in 1964 and has been available in the UK since 1967. In Europe and the United Kingdom (UK), MET has been used for almost any gastrointestinal symptom which might be related to motility: from heartburn to

diarrhea or from nausea to belly cramps. Early in its history, MET was originally intended only for acute use as: an antiemetic, in diagnostic radiology, for duodenal intubation, and emergency anesthesia. MET was the new alternative to drugs such as prochlorperazine. Subsequently, MET has been used chronically for a variety of gastrointestinal complaints in the United States. Since cisapride has been removed from the U.S. market, MET is one of the few prokinetic agents available. The chronic use of MET for various gastrointestinal complaints can be expected to increase in the future, until a replacement for cisapride is found.

Reports of MET associated movement disorders

Between 1968 and 1984, MET was the most frequently reported cause of extrapyramidal disorders to the Committee on the Safety of Medicines in the UK. A summary of those reports is depicted in the following table.

During the same reporting period there were sixty-two reports of EPS associated with prochlorperazine use. [Mann, 1986]

Side Effect (n)	Drug	1964-78	1983	1964-84
Akathisia (17)	Metoclopramide	5		12
EPS (134)		246	9	329
Oculogyric crisis (38)		46	6	90
Tremor (17)		7	0	14
Dyskinesia (39)		2	1	15
Dystonia (49)		37	15	80

Adapted from (Mann, 1986)

The original package insert in the United States contained the following language:

“Extrypyramidal reactions” occur in only one of 500 patients treated with MET” (AH Robbins, 1986)

Apparently, they were referring to the single dose use of injectable MET in patients with adequate renal function.

By the time Miller and Jankovic published their review on MET induced movement disorders at least 1031 patients had been described. (Miller, 1989) They included 16 patients (maximum MET dose 20-40 mg/day) referred to their movement disorder clinic at Baylor. The average duration of exposure to MET prior to onset of the movement disorders was 12 months. The range of exposures was from one day to 48 months. MET therapy was continued for an average of six months after the onset of symptoms, reflecting the clinical non-recognition of the movement disorder and its relationship to MET. In only one of their 16 patients was the problem recognized as MET induced movement disorder by the referring physician. In their experience, MET induced movement disorders are typically found within the first three months of MET therapy. The parkinsonian features associated with MET resolve in most patients within 60 days after drug therapy is discontinued. However, the recovery period may range from a few days to 365 days.

Sethi and colleagues found six cases of MET associated parkinsonism due to chronic therapy in their practice

over a two year period. (Sehti, 1989) Clinical features in their case series which were inconsistent with idiopathic Parkinson's disease included: bilateral onset in five of six cases and rapid progression. One of their cases was described in detail:

69 Year-old black female with a history of insulin-dependent diabetes mellitus, gout, hypertension, status post myocardial infarction and duodenal ulcer. MET therapy was begun for nausea and vomiting associated with gastroparesis. After two months she began to notice difficulty with her gait, her activity diminished, and over the next month she became bedridden. On physical examination the findings included: low volume speech, mask-like facies, resting tremor in the upper extremities-diminished with movement, cogwheel rigidity in all four extremities, stooped posture, postural instability, and inability to walk. Nine days after MET was discontinued the tremor had resolved, rigidity had moderated, but the mask-like facies and low-volume speech pattern persisted. Postural instability was no longer a problem. At follow-up 60 days later her gait, facial expression and speech had improved markedly.

Grimes and colleagues, at the Parkinson's Disease Clinic, University of Ottawa, described 18 patients with MET induced movement disorders seen over a two year period. (Grimes, 1982) Twelve of their patients aged 59-73 years, had parkinsonism, with tremor, rigidity and bradykinesia. They had been receiving MET orally 15-40 mg/day for periods ranging from two weeks to four years. In 10 of them, the disorder had been misdiagnosed as classic Parkinson's disease and six had been treated with levodopa for durations of three months to two years. One of their patients, a 73 Year-old male had been treated with multiple antiparkinson medications without improvement. When the MET and the antiparkinsonian medications were discontinued his bradykinesia and tremor cleared within two weeks. Facial movements typical of tardive dyskinesia worsened briefly after MET was discontinued, but resolved within two weeks.

Grimes and colleagues have also reported 12 cases of tardive dyskinesia associated with chronic MET therapy. (Grimes, 1982) The mean age of this group was 72 years, they had received MET at an average daily dose of 29 mg for between eight and 60 months. Mouth and facial movements typical of tardive dyskinesia developed during therapy or on MET withdrawal. In three patients the movements cleared within three weeks. Eight others had involuntary movements for periods ranging from six-36 months.

Case control study

By the 1990's reports of MET associated movement disorders had attracted the attention of the Harvard School of Public Health. Avorn and colleagues studied the effect of MET use in older patients on the subsequent use of antiparkinsonian therapy. (Avorn, 1995) Cases were Medicaid enrollees aged 65 years or older, newly prescribed levodopa (n=1253). The control group was 16,435 medicaid enrollees older than 65 years who did not use any antiparkinson therapy. MET users were three times more likely to begin use of a levodopa containing medication compared with nonusers. They concluded that MET use conferred an increased risk for the initiation of treatment usually reserved for idiopathic Parkinson's disease. They suspect this pattern of drug use may represent the misdiagnosis or Parkinson's disease or other Parkinson's plus syndromes in patients with drug-induced parkinsonian symptoms. In addition, the use of Sinemet™ in the setting of dopamine blockade is unlikely to benefit the patient, but it will add a risk of several iatrogenic syndromes including: hypotension, confusion, insomnia and GI distress. They suggest the use of other newer drugs, such as granisetron, to control emesis. However only erythromycin and dopamine blockers are available for use in gut motility disorders.

Case report: MET associated parkinsonism mimicking functional psychiatric illness

Maricle and Leung describe a 66 Year-old female who was hospitalized for almost three months with many complications and a tremor. She denied any psychiatric history, but since her recent procedures she had been: nervous, developed a tremor, had difficulty sleeping, experienced a variety of somatic symptoms, and a feeling of helplessness and hopelessness. On examination she displayed masked facies, bradykinesia, cogwheel rigidity, and a coarse, high-amplitude, bilateral pill-rolling tremor. Her Mini-Mental State examination results were normal. The provisional diagnosis was parkinsonism. The MET prescribed for post operative nausea and vomiting had not been stopped. MET was discontinued, four days later the tremor had lessened, her marked bradykinesia, tearfulness, and masked facies resolved. She denied any continuing feelings of nervousness, hopelessness or depression. Seven days after stopping MET she was discharged home much improved. (Maricle, 1989)

COMMENT:

Each component of the patient's syndrome and its resolution after MET withdrawal has been described in previously published case reports. By history, the patient's syndrome began after MET was started. His presentation was not consistent with Parkinson's disease and its rapid resolution after MET was withdrawn is not consistent with either Parkinson's disease or multiple system atrophy. Apparently neither the gastroenterologist, neurologist, nor the liaison psychiatrist considered the possibility of MET associated movement

disorder or depressive disorder before making their diagnosis of multiple system atrophy and major depressive disorder. His recent confusion and gastrointestinal complaints may have been related to his Sinemet™ therapy.

MET was suspected as a possible cause of his recent decline on admission to geriatric evaluation and management (GEM). His MET was withdrawn and over the following few weeks he was greatly improved. Because of the severity of his iatrogenic syndrome, the GEM team did not consider a rechallenge with MET advisable. His Sinemet™ therapy was also withdrawn. He was discharged home remarkably improved from his

condition on admission to Hospice with the belief that “he was dying.” He will be followed up in GEM clinic in one month, with plans to eventually discontinue his antidepressant therapy if none of the signs and symptoms of his major depressive disorder return.

The prevalence of neurological syndromes associated with chronic MET therapy is much higher than early clinical trial data would suggest. MET should be withdrawn in all patients who experience any of the neurological syndromes well known to occur with traditional neuroleptics.

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Mann RS. Drug induced disorders of central nervous function. In: D’Arcy PF and Griffin JP, editors. *Iatrogenic Disease*. 3rd ed. Oxford. *Oxford University Press*;1986. P. 586-650.

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Schulze-Delrieu K. Metoclopramide. *N Engl J Med*. 1981;305:28-33. (IDIS Article Number 133340)

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.

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 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.



Donna Brus, Editor

FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) <i>Trade Name</i>	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)*	Indication/Use	Valid <i>IDIS</i> Disease Term Modified ICD-9- CM Number
Anakinra (NA)** <i>Kineret</i>	Amgen, Inc. (Nov. 14)	ANAKINRA 14000405 (89 citations)	Reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients 18 years of age or older who have failed one or more disease modifying antirheumatic drugs (DMARDs).	Arthritis, Rheumatoid 714.0
Bosentan (1S***,V****) <i>Tracleer</i>	Actelion (Nov. 20)	BOSENTAN 24120050 (30 citations)	For treatment of pulmonary arterial hypertension.	Hypertension, Pulm, Prim 416.0
Desloratadine (1S) <i>Clarinet</i>	Schering-Plough (Dec. 21)	DESLORATADINE 4000001 (7 citations)	For relief of nasal and non-nasal symptoms of seasonal allergic rhinitis in patients 12 years and older.	Allergic Rhinitis NEC 477.
Drotrecogin Alfa, Activated (NA) <i>Xigris</i>	Lilly (Nov. 21)	DROTRECUGIN ALFA, ACTIVATED 20120437 (24 citations)	For reduction of mortality in adult patients with severe sepsis (sepsis associated with severe organ dysfunction) who have a high risk of death (e.g., as determined by APACHE II).	Septicemia NEC 038.
Dutasteride (1S) <i>Duagen</i>	GlaxoSmith Kline (Nov. 20)	DUTASTERIDE 10120165 (2 citations)	For treatment of signs and symptoms of benign prostatic hyperplasia.	Hyperplasia, Prostate 600.
Fondaparinux Sodium (1P)***** <i>Arixtra</i>	Fonda BV (Dec. 7)	FONDAPARIN 20120428 (24 citations)	For the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing hip fracture surgery, hip replacement surgery, and knee replacement surgery.	Embolism/Thrombosis, VN NEC 453. Prophylaxis NEC V07.
Frovatriptan (1S) <i>Frova</i>	Elan (Nov. 8)	FROVATRIPTAN 28081299 (4 citations)	For treatment of acute migraine attacks with or without aura in adults.	Migraine 346.
Nitisinone (1P,V) <i>Orfadin</i>	Swedish Orphan (Jan. 18)	NITISINONE 44100068 (4 citations)	An adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1.	Disorder, Amino Acid Metab 270.
Norelgestromin/Ethinyl Estradiol (1S) <i>Ortho Evra</i>	Ortho-McNeil (Nov. 20)	NORELGESTROMIN 68320007 ETHINYL ESTRADIOL 68160008 (13 citations)	For contraception.	Contraceptive Management V25.
Pimecrolimus (1S) <i>Elidel</i>	Novartis (Dec. 13)	PIMECROLIMUS 92000139 (12 citations)	For short-term and intermittent long-term therapy in the treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 2 years of age and older, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies.	Dermatitis, Atopic NEC 691.

* Through March 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.

New Drug Selected Bibliography

This new drug selected bibliography provides a selection of key clinical studies and reviews of new drugs approved by the FDA November 2001 through January 2002. *IDIS/CD-ROM* was searched to retrieve key articles relevant to the new drugs and their approved uses.

Anakinra

Bresnihan B, Alvaro-Garcia JM, Cobby M et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998;41:2196-2204. (*IDIS* Article Number 420783). ***In a double-blind, randomized, placebo-controlled multicenter study, investigators evaluated the efficacy and safety of a self-administered subcutaneous dose of anakinra at 30 mg, 75 mg, or 150 mg daily for 24 weeks in 472 patients with rheumatoid arthritis.***

Bosentan

Channick RN, Simonneau G, Sitbon O et al. Effects of the dual-endothelin receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo-controlled study. *Lancet* 2001;358:1119-1123. (*IDIS* Article Number 471290). ***In a twelve week, double-blind, randomized, placebo-controlled, multicenter study, investigators evaluated the efficacy and safety of bosentan (62.5 mg twice daily for 4 weeks, then 125 mg twice daily) in 32 patients with pulmonary hypertension (primary or associated with scleroderma). [ONE OF THE PIVOTAL STUDIES ON WHICH FDA APPROVAL WAS BASED.]***

Desloratadine

Geha RS and Meltzer EO. Desloratadine: a new, nonsedating, oral antihistamine. *J Allergy Clin Immunol* 2001;107:752-762. (*IDIS* Article Number 463345). ***This article is a comprehensive review of desloratadine.***

Goldman M and Quercia RA. Desloratadine: a once-daily nonsedating antihistamine for seasonal allergic rhinitis and chronic idiopathic urticaria. *Formulary* 2001;36:329-339. (*IDIS* Article Number 465078). ***This article is a comprehensive review of desloratadine.***

Drotrecogin Alfa, Activated

Bernard GR, Vincent JL, Laterre PF et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;699-709. (*IDIS* Article Number 461713). ***Investigators conducted a phase III randomized, double-blind, placebo-controlled multicenter trial to evaluate the efficacy and safety of drotrecogin alfa, activated (24 micrograms per kilogram of body weight per hour) for a total duration of 96 hours in 1690 patients with systemic inflammation and organ failure due to acute infection.***

Fondaparin

Eriksson BI, Bauer KA, Lassen MR et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med* 2001;345:1298-1304. (*IDIS* Article Number 471305). ***In a randomized, double-blind multicenter study, investigators compared once daily subcutaneous injection of fondaparinux (2.5 mg initiated postoperatively) to once daily subcutaneous injections of enoxaparin (40 mg initiated preoperatively) for the prevention of venous thromboembolism in 1711 patients undergoing surgery for hip fracture. [ONE OF THE PIVOTAL STUDIES ON WHICH FDA APPROVAL WAS BASED.]***

Bauer KA, Eriksson BI, Lassen MR et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med* 2001;345:1305-1310. (*IDIS* Article Number 471306). ***In a randomized, double-blind multicenter study, investigators compared the efficacy and safety of a once-daily subcutaneous injection of 2.5 mg fondaparinux with twice daily subcutaneous injections of 30 mg enoxaparin for the prevention of venous thromboembolism after elective major knee surgery in 1711 patients. [ONE OF THE PIVOTAL STUDIES ON WHICH FDA APPROVAL WAS BASED.]***

Nitisinone

Lindstedt S, Holme E, Lock EA et al. Treatment of hereditary tyrosinaemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase. *Lancet* 1992;340:813-7. (*IDIS* Article Number 303720). ***Investigators report the use of oral nitisinone (0.1-0.6 mg/kg daily) in one acute and four subacute chronic cases of hereditary tyrosinemia type I.***

IDIS/Web Feedback Option

IDIS/Web Evaluation Form

1. Did you find the information that you were looking for? Yes No

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If you had difficulty, please tell us about your computer system setup.

4. Do you have any comments or suggestions?

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We have included a 'feedback' option on the logout page of IDIS/Web. This addition gives the users of IDIS/Web an opportunity to let us know how well IDIS/Web is working, or what difficulties have been encountered in conducting a search. This feedback is intended to help us assess areas of IDIS/Web that might be enhanced.

The new feedback option can also be used to let us help with a search strategy. If you encounter difficulties in searching or are unable to retrieve the results you expect, the feedback form can be used to contact IDIS staff for help. Simply fill out the feedback form, indicating the topic of the search and the nature of the difficulty that was encountered. The comment section can also be used to communicate relevant details of the search strategy. Be sure to include your email address so that we can reply.

Upon receiving feedback forms from IDIS/Web users that request search help, IDIS staff will construct search strategies, conduct searches and view the results that are returned. The search strategy that obtained the best results will then be emailed to the user.



Nicola Sarrazin, R.Ph., Pharm.D.

New Journal Category and Journal Additions

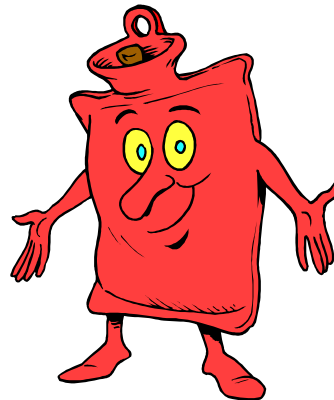
Effective January 2002, four new journals have been added to the database. Additionally, a new journal category, "Pain Management," has been designated to group the journals according to their subject area. One existing journal already being indexed, *Journal of Pain & Symptom Management*, has been moved from the Neurosciences category to the new Pain Management category. The four new journals are:

American Journal of Pain Management
(Journal Abbreviation: AM J PAIN MANAGE,
Frequency: Quarterly)

Headache (Journal Abbreviation: HEADACHE,
Frequency: Irregular-10/yr.)

International Journal of Acute Pain Management
(Journal Abbreviation: INT J AC PAIN MANAGE,
Frequency: Quarterly)

Pain (Journal Abbreviation: PAIN,
Frequency: Monthly)



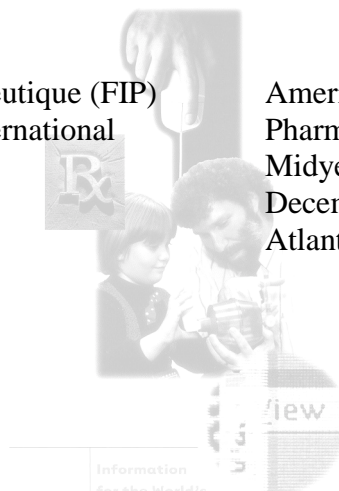
2002 EXHIBIT SCHEDULE

American Association of Colleges of Pharmacy
(AACCP) Annual Meeting
July 12 - 17, 2002
Kansas City, MO

American College of Clinical Pharmacy
(ACCP)
October 20 - 23, 2002
Albuquerque, NM

Federation Internationale Pharmaceutique (FIP)
Pharmacy World Congress and International
Congress of FIP
August 31 – September 5
Nice, France

American Society of Health-System
Pharmacists (ASHP)
Midyear Clinical Meeting (MCM)
December 8 - 12
Atlanta, GA



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