



Current Issues Related to Therapeutic Drug Monitoring: Aminoglycosides

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IN THIS ISSUE

- 1 CURRENT ISSUES RELATED TO THERAPEUTIC DRUG MONITORING: AMINOGLYCOSIDES
- 5 CE ASSESSMENT QUESTIONS
- 6 KEY REFERENCES FOR NEW DRUGS
- 7 NEW FDA APPROVALS
- 8 QUICK GUIDE TO DDIS PRODUCTS AND SERVICES
- 9 PERSPECTIVE FROM AN IDIS SUBSCRIBER: DIPHENHYDRAMINE IN CANCER PAIN
- 12 EXHIBIT SCHEDULE

Learning Objectives:

1. Explain the relationship between efficacy and aminoglycoside concentration.
2. Describe the therapeutic window for the aminoglycosides.
3. List the criteria for when it is appropriate to measure aminoglycoside drug concentrations.
4. List the criteria for when conventional and pulse dosing of aminoglycosides is appropriate.
5. List optimal drug sampling times for aminoglycosides if therapeutic drug monitoring is done.

Introduction

Achieving target antibiotic concentrations is a challenge for aminoglycosides when patients are continuously changing. It is equally challenging for the health care professional to keep up with current monitoring recommendations for these antibiotics and current dosing approaches.

Relationship Between Serum Concentration and Efficacy

Minimum inhibitory concentration (MIC) is the most widely used laboratory parameter in making decisions on antimicrobial choice. (Dipiro, 1999) It is the lowest antimicrobial concentration that prevents visible growth of an organism after 24 hours of incubation in a specified growth medium. (Dipiro, 1996, 1999 and McDonald, 1981) The MIC for the gram-negative pathogens that are susceptible to gentamicin has a range from 0.5 to 2 mg/L. For example, MIC of *E. coli* is 1-1.5 mg/L and MIC of *Pseudomonas aeruginosa* is 1-2 mg/L. (Zaske, 1992) Aminoglycosides have both a concentration-dependent bactericidal activity and a concentration-dependent post-antibiotic effect against many pathogens. (Vogelman 1986) The pharmacodynamic principle behind the concentration-dependent bactericidal activity is a maximization of serum peak concentration (C_{max})-to-MIC ratio. The gentamicin concentration-dependent killing activity reaches greater killing with increasing increments of concentration. (Dipiro, 1999) According to Moore and coworkers (1987), a ratio of ten or more for C_{max} :MIC is necessary to achieve a 90% effect when treating with gentamicin. Therefore, a large C_{max} -

to-MIC ratio has been associated with a positive clinical response.

Post-antibiotic effect (PAE) is the persistent suppression of bacteria growth after exposure and removal of an antibiotic. (Dipiro, 1999) In general, PAE is established by exposing bacteria of a fixed inoculum to an antibiotic. The difference in time that it takes the bacteria exposed to the antibiotic to grow ten fold compared to a separate culture of bacteria processed the same way and not subjected to the antibiotic is the PAE. (Dipiro, 1999) The exact mechanism for PAE is not known, but there are some possible explanations. The PAE of aminoglycosides may be due to sublethal amounts of drug binding to bacterial ribosomes and disrupting protein synthesis. Furthermore, the PAE may represent the time needed for ribosomal synthesis of proteins to resume after exposure to the antibiotic. (Vogelman, 1988) Hence, as a general rule, antibiotics that inhibit DNA or protein synthesis of bacteria demonstrate a significant PAE effect against gram-negative bacteria. (Dipiro, 1999) For many bacteria, the PAE appears to be more prolonged in vivo than in vitro. One explanation is the contribution of the host immune response aiding in the control of bacterial cell division or lower rate of bacterial growth in animal models than in broth cultures. (Rodman, 1994)

Higher serum aminoglycoside levels are not only related to better bactericidal activity but a longer PAE effect. The combination of PAE and a large ratio of C_{max} to MIC increases the effectiveness of aminoglycoside therapy. This may explain the

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Accreditation Information

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effectiveness of the treatment of aminoglycosides when used once a day.

Therapeutic Window Effectiveness/ Toxicity

A narrow therapeutic window implies that there is a small range for drug levels to fall between to allow the drug to remain therapeutic and yet not be toxic. The two most common toxicities associated with the aminoglycosides are ototoxicity and nephrotoxicity.

Ototoxicity and nephrotoxicity are both thought to be related to serum concentration for the aminoglycosides. Ototoxicity is generally irreversible or only partially reversible. Nephrotoxicity is generally reversible when the drug is discontinued or is carefully monitored and the serum concentrations are controlled. (Zaske, 1992) The possible mechanism by which aminoglycosides cause nephrotoxicity has been extensively studied. (De Broe, 1984; Giuliano, 1984, 1986, 1986a, 1986b; Silverblatt, 1979) Chronically elevated trough levels are a greater risk for developing this type of toxicity.

Nephrotoxicity secondary to the use of aminoglycosides generally occurs at least five days after the initiation of therapy. (Mondorf, 1978) Sustained trough levels above 2 mg/L are a greater risk for nephrotoxicity, than high peak levels. Typical findings include decreased glomerular filtration rate, increased serum creatinine, increased blood urea nitrogen, and impaired urinary concentration ability. Additionally, symptoms may include proteinuria, aminoaciduria, and electrolyte disturbances. A significant increase in serum creatinine is an indicator of aminoglycoside nephrotoxicity. In most of the clinical studies, a change in serum creatinine of 0.5 mg/dL or greater is defined as a significant change and indicates nephrotoxicity. (Zaske, 1992)

There is less information available about the relationship between aminoglycoside disposition and the development of ototoxicity.

This is largely due to a lack of animal models for cochlear and vestibular damage. (Marra, 1996) Animal studies suggest that short term exposure to high serum aminoglycoside concentration does not cause excessive accumulation of drug in the ear. (Ohtani, 1982) Some factors which may be associated with aminoglycoside ototoxicity include cumulative dose, average daily dose, peak serum concentration, trough concentration, concurrent diuretics such as furosemide or ethacrynic acid, underlying disease state, and previous exposure to aminoglycoside treatment. (Moore, 1984) Elderly patients apparently have a higher risk of toxicity than do pediatric patients. (Zaske, 1992)

Based on this toxicity information and the previous efficacy information it is desirable to ensure that aminoglycoside peak concentrations achieve high C_{max} -MIC ratios (10 or greater), but allow troughs to fall below 1-2 mg/L before re-dosing. In conventional dosing peak concentrations of 6-10 mg/L and trough concentrations of less than or equal to 2 mg/L are advocated for gentamicin, tobramycin and netilmicin, with double these values for amikacin. (Begg, 2001) Therapeutic ranges in extended interval dosing are not relevant. Peak concentration will always be in excess of those seen in conventional dosing and within bactericidal range. Trough concentrations are also unnecessary because concentrations at the end of the extended interval should be near zero or at least undetectable using conventional assays.

Dosing Regimens

Dosing regimens for aminoglycosides can be classified as conventional or extended interval dosing (once daily dosing) also referred to as pulse dosing. Conventional dosing gives the aminoglycoside in divided doses every 8-12 hours. Typically gentamicin is given 3-5 mg/kg/day to adults and for children, due to their larger clearance, is given, 6-7.5 mg/kg/day. (American Society of Hospital Pharmacists, 2000) The wide variability in elimination half-life of gentamicin has led some people to prospectively dose the drug using population estimates of volume of distribution and elimination rate constant. (Zaske, 1982) Dose adjustment is frequently done retrospectively according to a person's response to gentamicin and his/her renal function. These dosage adjustments are made on the basis of a measured peak and trough concentration. In addition, various nomograms and Bayesian forecasting programs have been successfully used to initiate therapy. (Begg, 1995a) and (Zaske, 1992)

Pulse dosing involves administering the drug in a larger dose with an extended interval before the next dose. The dosing interval generally falls between 24 and 48 hours. Nicolau and coworkers (Nicolau, 1995) established a popularly used dosing guideline. The suggested dose is 7 mg/kg and dosing intervals are dependent upon renal function as estimated by creatinine clearance (Cl_{cr}). Patients with Cl_{cr} more than 60 ml/min are administered gentamicin every 24 hours while those with Cl_{cr} 40 to 60 ml/min, receive the drug every 36 hours and patients with Cl_{cr} 20 to 40 ml/min receive it every 48 hours. For patients whose Cl_{cr} is less than 20 ml/min the conventional dosing approach should be used.

Extended interval dosing has become popular because the significantly higher peak levels relate to enhanced therapeutic outcomes. In addition, this approach results in lower trough concentrations which may result in the decreased risk of toxicity. Extended interval dosing can cost less mainly due to reduced serum drug level monitoring, pharmacist preparation time and nursing administration time. (Periti, 1995) An outcome study (Nicolau, 1996)

demonstrated that the pulse dosing regimen of gentamicin is 9-37% less expensive than the multiple dose regimen.

Once daily dosing should not be applied to the pediatric population, patients with bacterial endocarditis or patients with a creatinine clearance of less than 20 ml/min. (Begg, 1995b) Begg (1995a) reports that there have been at least 29 studies in humans comparing once daily aminoglycoside administration with conventional treatment. Twenty-two failed to show any difference in efficacy or toxicity. Seven studies demonstrated a difference in favor of once daily dosing. One study demonstrated better efficacy in the once daily group. Of six studies demonstrating less toxicity in the extended interval group, five showed less nephrotoxicity and two showed less ototoxicity. No study has shown a clear advantage for the conventional approach.

Infusion Considerations

Although aminoglycosides can be given by bolus administration, Zaske. (1992) recommended that infusions be given over 30 to 60 minutes. Streetman and coworkers (2001) and Van Lent-Evers (1999) in their recent evaluation of individualized pharmacokinetic dosing utilized 30 minute infusions. Nicolau and coworkers (1995) infused a large extended interval dose over a 60 minute period.

Sampling Recommendations

Drug levels that are utilized to make pharmacokinetic dosage adjustments must be correctly and accurately obtained. (Herman, 2002) Failure to do so can result in dangerous and inappropriate adjustments in drug therapy.

Serum levels and recommended times to take levels vary depending on whether conventional or pulse dosing is used. Sampling times for peak concentrations in conventional dosing are 60-90 minutes after IM injection and 30-60 minutes after IV infusion. (Hammett-Stabler, 1998) This should allow the initial rapid distribution phase of the aminoglycoside (half-life of 5-15 minutes (Anderson, 1999) to be complete before the peak is obtained. Trough levels are to be taken immediately before the next dose. In the review by Begg and coworkers (2001), peak sampling times were recommended at least 30 minutes after the infusion and troughs within 30 minutes of the next dose. MacGowan and Reeves (1994) proposed measurement of a single serum level sample at 8 hours post infusion to make dosage adjustments for extended interval dosing. The Nicolau nomogram (Nicolau, 1995) recommends a single serum level sample drawn any time from 6 to 14 hours following the start of the 60 minute infusion.

...it would be desirable to ensure that aminoglycoside concentrations be targeted to allow the peak concentrations to achieve high C_{max} - MIC ratios ... but allow the trough to fall below 1-2 mg/L...

There are two practical issues to discuss. First, if a trough is obtained within 30 minutes of the next dose it can be assumed that it was obtained immediately before the next dose. The fall in concentration of the trough over that 30 minute period will in almost all cases be undetectable. Second, it is common practice to measure trough and peak around the administration of a dose. If steady state has been achieved (therapy was initiated at least 5 half-lives before the measurements are made), then the pre-dose trough can be extrapolated to a post-dose

trough. Care must be made to do pharmacokinetic calculations based on the extrapolated trough. This approach will decrease the number of errors associated with sample collection, but can increase pharmacokinetic calculation errors if care is not exercised.

The frequency of monitoring is also important. Generally, the clinical situation and patient specific factors should guide frequency of sampling. An otherwise healthy patient with normal renal function may not need to be monitored closely. It may be sufficient to monitor aminoglycoside levels once a week if a patient will be on the antibiotic for an extended period of time. However, there are populations of people who do need to be monitored more closely. These are often the patients where it may be more appropriate to use conventional therapy instead of extended interval therapy. These populations include the elderly, anephric patients, patients with creatinine clearance below 20 ml/min/1.73 m², patients undergoing dialysis with high flux filter membranes, concomitant nephro- or oto-toxic medications (like amphotericin B, furosemide, ethacrynic acid, or vancomycin), patients with rapidly changing renal function, malignancy, obesity and intensive care situations. (Begg, 2001) It is also important to monitor serum creatinine concentrations as a marker for the development of nephrotoxicity, although often the drug levels will rise before the serum creatinine does.

Drug levels that are utilized to make pharmacokinetic dosage adjustments must be correctly and accurately obtained.

Conclusion

Current evidence suggests that when possible extended interval or pulse dosing of aminoglycosides has significant therapeutic and economic advantages. With this dosing approach there is no therapeutic window for drug concentrations. A single drug level should be obtained 6 to 14 hours after the start of the 60 minute infusion. The dosing interval is then adjusted based upon this level. There are a number of situations where this approach is not recommended and a conventional dosing approach should be utilized. With this approach, the therapeutic drug monitoring goal is to achieve steady state peak concentrations 30 minutes after a 30 minute infusion in the range of 6-10 mg/L. The steady state trough should be 1-2 mg/L. On the average, steady state will be reached by the third dose, so it is often around the third dose that the peak and trough are obtained. In a patient with stable renal function it is usually sufficient to monitor levels once every seven days. It is advisable to monitor renal function every three days while the patient is on the aminoglycoside.

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(circle the correct answer)

CE REGISTRATION

TITLE OF EDUCATIONAL ACTIVITY (ARTICLE)

Current Issues Related to Therapeutics Drug Monitoring: Aminoglycosides
ACPE # 020-000-02-026-H01

NAME _____
 ADDRESS _____
 CITY _____ STATE _____ ZIP _____
 SOCIAL SECURITY NUMBER _____
 PHARMACY LICENSE NUMBER(S) _____

I HEREBY CERTIFY THAT I HAVE TAKEN THIS TEST:

 Signature/Date

1. Aminoglycosides exhibit concentration-dependent bactericidal activity. As a result, it is important to:

- Maintain the trough concentration at the MIC for the organism.
- Maintain the trough concentration 4-5 times the MIC for the organism.
- Achieve a high peak concentration (C_{max}) to MIC ratio.
- Keep the area under the curve for a dosing interval ten times the MIC.

2. Which of the following statements is **not true** about the post-antibiotic effect (PAE) of aminoglycosides?

- The PAE is the persistent suppression of bacterial growth even when the antibiotic is no longer present.
- The PAE appears to be more prolonged *in vitro* than *in vivo*.
- The host immune response enhances the PAE.
- The PAE enhances the effectiveness of aminoglycosides when using extended interval dosing.

3. Which one of the following is **true** about ototoxicity:

- The cumulative dose of aminoglycoside does not appear to be related to ototoxicity.
- Hearing loss is generally fully reversible.
- The elderly are more susceptible than pediatric patients.
- Concurrent use of furosemide has no effect on ototoxicity, only on nephrotoxicity.

4. Which one of the following is **true** about nephrotoxicity:

- Nephrotoxicity is generally reversible when the drug is discontinued.
- It generally appears immediately after initiation of therapy.
- Chronically elevated peaks are more likely to develop nephrotoxicity.
- Typically glomerular filtration increases and urine becomes very concentrated.

5. Which one of the following statements is **not true** about the therapeutic window for aminoglycosides:

- it is desirable for peak concentration to achieve a C_{max} : MIC ratio > 20.
- The trough concentration must be below 2 mg/L.
- For conventional dosing, the peak concentration should be 6-10 mg/L.
- For extended interval dosing, the peak concentration should be 20-30 mg/L.

6. Which one of the following is **not true** about extended interval (pulse) dosing?

- A single concentration is measured 6-14 hours after the initial dose to determine an optimal dosing interval.
- This dosing approach tends to be more expensive.
- At least one study has shown increased efficacy over conventional dosing.
- At least six studies have shown reduced nephro- or ototoxicity with this approach.

7. Which one of the following is **not true** about conventional dosing:

- There is wide variability in the distribution and elimination of the aminoglycosides.
- Empiric dosing (3-5 mg/Kg), or dosing based on nomograms, or using population based pharmacokinetic estimates or Bayesian forecasting all have been used successfully to initiate therapy.
- Children have a higher clearance of the drug and therefore need a lower dose when dosing by weight.
- No studies have shown a clear advantage of this dosing approach over pulse dosing.

8. The following are all situations when extended interval dosing should **not** be used **except**:

- Pediatric patients.
- In bacterial endocarditis.
- A patient with an acute appendicitis is also on amphotericin B.
- A diabetic ulcer patient with Cl_{cr} of 40 ml/min.

9. If peak samples are measured following conventional dosing, the main reason samples are measured 30-60 minutes after an infusion is:

- To give nursing staff time to get the collection tube and paperwork ready.
- To allow the drug that is still in the IV tubing to get into the body.
- Because it is not wise to sample during the first half-life of the drug elimination.
- To allow the initial distribution phase to be complete before monitoring the elimination of the antibiotic.

10. Monitoring aminoglycoside therapy should include all of the following **except**:

- Patients on amphotericin B, furosemide or ethacrynic acid require more intensive monitoring.
- Liver failure patients will require more intense monitoring.
- Monitor renal function every 3 days.
- Normally it is not necessary to monitor aminoglycoside levels more than once every 7 days if renal function is stable.

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 | |
| Increased my knowledge | 5 | 4 | 3 | 2 | 1 | |
| Achieved stated objectives | 5 | 4 | 3 | 2 | 1 | |
| Was educational and not promotional | 5 | 4 | 3 | 2 | 1 | |

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

New Drugs: Key References

This new drug selected bibliography provides a selection of key clinical studies and reviews of new drugs approved by the FDA May 2002 through August 14, 2002. IDIS was searched to retrieve key articles relevant to the new drugs and their approved uses.

Escitalopram

Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry* 2002;63:331-336. (IDIS Article Number 479908) **Efficacy and tolerability of escitalopram were evaluated in 491 patients with major depressive disorder (MADRS minimum score=22) in this double-blind, randomized, placebo-controlled multicenter trial, in which patients were randomly assigned to placebo, escitalopram 10 mg/day or 20 mg/day or citalopram 40 mg/day.**

Oxaliplatin

Scheithauer W, Kornek GV, Raderer M, Ulrich-Pur H et al. Randomized multicenter Phase II trial of oxaliplatin plus irinotecan versus raltitrexed as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2002;20:165-172. (IDIS Article Number 475043) **In this randomized, multicenter, Phase II trial, 92 patients with colorectal cancer were randomized to receive infusions of oxaliplatin 85 mg/m² plus irinotecan 175 mg/m² biweekly or raltitrexed 3 mg/m² on one day every three weeks.**

De Gramont A, Figer A, Seymour M, Homerin M et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;18:2938-2947. (IDIS Article Number 451785) **This Phase III randomized trial investigated the efficacy of combining oxaliplatin with leucovorin and fluorouracil and included 420 previously untreated patients with colorectal cancer who were randomized to either leucovorin 200 mg/m²/d followed by bolus 5FU 400 mg/m²/d and 22-hour infusion of 600 mg/m²/d for 2 consecutive days every two weeks, alone or with a 2-hour infusion of oxaliplatin 85 mg/m² on day 1.**

Rasburicase

Goldman SC, Holcberg JS, Finklestein JZ, Hutchinson R et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood* 2001;97:2998-3003. (IDIS Article Number 463743) **This study was a multicenter randomized trial with the established primary end point for efficacy as the area under the serial plasma uric acid concentration curves during the first 96 hours of therapy, comparing rasburicase (0.20 mg/kg infused over 30 minutes) to allopurinol (10 mg/kg divided every 8 hours) in 52 pediatric patients with leukemia or lymphoma at high risk for tumor lysis.**

Pui CH, Mahmoud HH, Wiley JM, Woods GM et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. *J Clin Oncol* 2001;19:697-704. (IDIS Article Number 460147) **In a comparative cohort study evaluating the safety and efficacy of rasburicase, 131 children, adolescents and young adults (age range 0.08-20 years) diagnosed with leukemia or lymphoma and with abnormally high plasma uric acid concentrations or large tumor cell burden, were administered intravenous rasburicase at doses of 0.15 or 0.20 mg/kg for 5-7 consecutive days.**

Tegaserod

Fidelholtz J, Smith W, Rawls J, Shi Y et al. Safety and tolerability of tegaserod in patients with irritable bowel syndrome and diarrhea symptoms. *Am J Gastroenterol* 2002;97:1176-1181. (IDIS Article Number 480878) **Investigators conducted a double-blind, placebo-controlled randomized 8-week trial of tegaserod at doses of 4 mg or 12 mg a day or placebo in 86 patients with irritable bowel syndrome to assess complications of diarrhea.**

Prather CM, Camilleri M, Zinsmeister AR, McKinzie S, Thomforde G. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. *Gastroenterology* 2000;118:463-468. (IDIS Article Number 444335) **Twenty-four patients with constipation-predominant irritable bowel syndrome were randomized to oral administration of tegaserod, 2 mg twice daily, or placebo for one week with gastric emptying, small bowel and colonic transit measured before and after one week of administration of the study drug.**

Treprostinil

Simonneau G, Barst RJ, Galie n, Naeije R et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2002;165:800-804. (IDIS Article Number 480255) **This was a 12-week, double-blind, placebo-controlled multicenter trial to determine the safety and efficacy of a continuous subcutaneous infusion of treprostinil in 470 patients with pulmonary hypertension, either primary or associated with connective tissue disease. [A PIVOTAL STUDY ON WHICH FDA APPROVAL WAS BASED.]**

Voriconazole

Denning DW, Ribaud P, Milpied N, Caillot D et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002;34:563-571. (IDIS Article Number 476865) **In an open, noncomparative multicenter study, investigators evaluated the use of voriconazole (intravenously 6 mg/kg twice a day two times, 3 mg/kg twice a day for 6-27 days, then orally at 200 mg twice a day for up to 24 weeks) in 116 immunocompromised patients with invasive aspergillosis.**



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FDA DRUG/BIOLOGIC APPROVALS

| Generic Name (FDA Therapeutic Classification) Trade Name | Sponsor (Approval Date) | Valid IDIS Drug Term Drug Number (IDIS Citations)* | Indication/Use | Valid IDIS Disease Term Modified ICD-9-CM Number |
|---|---|---|---|--|
| Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) <i>Daptacel</i> | Aventis Pasteur Ltd. (May 14) | DIPHTHERIA-ACELL PERTUS-TET 80120049 (254 citations) | Active immunization of infants and toddlers at 2, 4, 6, and 17-20 months of age against diphtheria, tetanus and pertussis. | Diphtheria 032. Whooping Cough 033. Tetanus 037. |
| Escitalopram Oxalate <i>Lexapro</i> | Forest Laboratories, Inc. (Aug. 14) | ESCITALOPRAM 28160711 (1 citation) | Indicated for the treatment of major depressive disorder. | Disorder, Depressive NEC 311. |
| Oxaliplatin <i>Eloxatin</i> | Sanofi-Synthelabo, Inc. (Aug. 9) | OXALIPLATIN 10040808 (73 citations) | For use in combination with infusional 5- flourouracil (5-FU) and leucovorin for the treatment of patients with colorectal cancer whose disease has recurred or become worse following initial therapy with a combination of irinotecan with bolus 5-FU and leucovorin. | NEOP, MGN-Rectosigmoid Junct. 154.0 |
| Perflexane Lipid Microspheres (1S) <i>Imagent</i> | Alliance (May 31) | PERFLEXANE 36000041 (45 citations) | Ultrasound imaging agent for use in subjects with a suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. | Ultrasound, Diagnostic 88.7 |
| Rasburicase <i>Elitek</i> | Sanofi-Synthelabo, Inc. (July 12) | RASBURICASE 2000004 (2 citations) | Initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid. | Leukemia NEC 208. NEOP, MGN-Lymph/Histio NEC 202. Abnormality, Blood Exam 790. |
| Sodium Oxybate (1P) <i>Xyrem</i> | Orphan Medical Inc. (July 17) | SODIUM OXYBATE 28240849 (74 citations) | Treatment to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy. | Cataplexy and Narcolepsy 347. |
| Tegaserod maleate (1P) <i>Zelnorm</i> | Novartis Pharmaceuticals Corp. (July 24) | TEGASEROD 56400031 (16 citations) | Treatment of women with irritable bowel syndrome whose primary bowel symptom is constipation. | Irritable Colon 564.1 |
| Treprostinil (1P, V) <i>Remodulin</i> | United Therapeutics (May 21) | TREPROSTINIL 20120668 (5 citations) | Synthetic prostacyclin analog for treatment of pulmonary arterial hypertension in patients with NYHA class II-IV symptoms to diminish symptoms associated with exercise. | Hypertension, Pulm, Prim 416.0 |
| Voriconazole (1S) <i>Vfend</i> | Pfizer (May 24) | VORICONAZOLE 8120520 (53 citations) | Antifungal for treatment of invasive aspergillosis and for treatment of serious fungal infections caused by the pathogens <i>Scedosporium apiospermum</i> and <i>Fusarium</i> spp including <i>Fusarium solani</i> , in patients intolerant of or refractory to other therapy. | Mycosis NEC 117. Aspergillosis 117.3 Allescheriosis 117.6 |

* Through August 2002 Update. Complete bibliographic citations will be provided upon request.

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

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RAPID RESPONSE TO ALL REQUESTS.

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RAPID RESPONSE
EVIDENCE BASED EVALUATION



Re: Use of diphenhydramine as an analgesic in refractory cancer pain.

DATA:

VITALS — 181 lbs (01/18/02), temperature 100.7 (01/23/02), respiratory rate 20 (01/23/02), pulse 74 (01/23/02), blood pressure 108/57 (01/23/02) LABS — (05/23/02) sodium 145, potassium 4.2, liver function tests - within reference ranges, (blood urea nitrogen) BUN/s, creatinine 57/2.9

MEDICATIONS:

On admission to Hospice - albuterol by nebulizer four times per day, ipratropium by nebulizer four times per day, citalopram 20 mg per nasogastric tube every day, diazepam 5 mg per nasogastric tube twice a day, diazepam 5 mg per nasogastric tube twice a day as needed, methadone 10 mg per nasogastric tube every 8 hours, morphine sulfate 15 mg by nebulizer four times daily as needed, morphine sulfate 20 mg/ml (oral solution) 20-40 mg per nasogastric tube every 3 hours as needed, morphine sulfate 20 mg/ml (oral solution) 30 mg per nasogastric tube every 4 hours as needed breakthrough pain.

HISTORY OF PRESENT ILLNESS:

The patient was seen in September 2001 and noted to have a right vocal cord lesion. One month later he was biopsied and found to have squamous cell carcinoma of the larynx, stage IV. He presented in December 2001 with stridor and required an operative tracheostomy. Subsequently he began a combined radiotherapy and chemotherapy regimen. He completed the radiotherapy portion of the regimen, but only the first of three planned courses of chemotherapy. In May 2002 he presented to the emergency room with difficulty breathing. During that admission his tracheostomy repeatedly plugged and his pain was uncontrolled. He was admitted to hospice for comfort care on May 15th.

PRIOR MEDICAL HISTORY:

Nicotine dependence, hepatitis, alcohol dependence, in remission,

chronic obstructive pulmonary disease, emphysema, and anemia.

HOSPICE COURSE:

He was awake and alert on transfer to hospice on May 22nd. He experienced significant pain during his tracheostomy care. His transdermal fentanyl plus oral morphine for breakthrough pain regimen was discontinued. A continuous morphine infusion was started at a rate of 7 mg per hour. He was also receiving IV haloperidol and lorazepam as needed for agitation.

Over the next one to two weeks he was noted to be extremely restless and anxious. Occasionally he would attempt to go over the bed rails. By this time his morphine infusion rate had been increased to 39 mg per hour. He was also requiring frequent IV lorazepam boluses, as problems with secretions into his tracheostomy increased. Eventually his morphine infusion rate was increased to 120 mg per hour plus boluses during each shift. By June

26th his morphine infusion rate was increased to 190 mg per hour and he was requiring several morphine boluses each shift for pain control. His breathing became more difficult and he was described as quite restless and agitated when thick mucus secretions accumulated in his tracheostomy tube.

IV Benadryl™ 25 mg was begun every six hours in the early evening on June 26th. After the diphenhydramine was begun he was more comfortable and did not require as many additional morphine boluses as in the recent past. The amount of mucus secretion declined and he has required less frequent suctioning of this tracheostomy to clear mucus plugs. On June 27th the Benadryl™ was increased to 50 mg IV every six hours.

On June 28th his morphine infusion was converted to a subcutaneous hydro-morphine infusion infusing at 25 mg/hour. The combination of intravenous diphenhydramine and subcutaneous hydromorphone with infrequent as

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needed bolus doses of hydromorphone were associated with less agitation, restlessness and pain until his death on July 4th.

LITERATURE:

Since the late 1930's it has been speculated that histamine might be a mediator of cutaneous pain. Raffa has recently commented on the role of histamine in pain and on the preclinical and clinical data suggesting that some antihistamines have analgesic activity. (Raffa, 2001) Rumore and Schlichting (1985, 1986) have authored reviews on preclinical data and proposed mechanism of action and the clinical efficacy of antihistamines as analgesics. They believe there is considerable evidence supporting an analgesic effect of various antihistamines. For those readers interested in a discussion of the various speculative mechanisms proposed for the analgesic action of antihistamines the Life Science review is recommended. Those readers interested in the clinical details of reports of analgesic efficacy will find the Pain review useful.

Single ingredient studies, included in the review published in the journal *Pain*, have described analgesic efficacy for hydroxyzine, diphenhydramine, orphenadrine, pyrilamine and several other compounds not marketed in the United States as antihistamines. The antihistamines are unrelated chemically or

pharmacologically to opioids or non-steroidal anti-inflammatory agents. They appear to be safe with little or no respiratory depression or gastrointestinal adverse reaction profile. Gherlardini (1998) and colleagues reported that tolerance did not develop to the antinociceptive effect of diphenhydramine, promethazine, or pyrilamine in mice after fourteen days of treatment. Tolerance is readily demonstrated to the antinociceptive effects of opioids in animal models.

The successful use of diphenhydramine as a local anesthetic has been described by several groups. Pollack and Swindle (1989) used diphenhydramine 1 percent with and without epinephrine by local infiltration prior to suturing lacerations in three women. In all three women anesthesia was achieved within 5 minutes as judged by insensitivity to pinprick. The duration of anesthesia was approximately 30 minutes, and the lacerations were repaired without discomfort. Ernst and associates (1993) studied ninety-nine patients who received diphenhydramine 1 percent or lidocaine 1 percent for the repair of simple lacerations in a double blind trial. (Ernst, 1993) On a visual analog scale patients reported a median pain score of 2 (mild pain) after lidocaine and 4 (moderate pain) after diphenhydramine. The authors concluded that diphenhydramine was a viable alternative for patients with allergy to local anesthetics.

Santiago-Palma and colleagues (2001) have recently described three patients with advanced cancer pain who had failed previous

trials with different opioids and adjuvants but subsequently obtained pain relief after administration of diphenhydramine. The first patient was a 71 year-old female who had stage IV non-small cell lung cancer with a 2.5 year history of worsening right-sided chest wall pain. She had failed or been intolerant to previous pain regimens including oral morphine, transdermal and parenteral fentanyl, parenteral methadone, epidural fentanyl, clonidine, and bupivacaine, lidocaine patches, amitriptyline and gabapentin. Diphenhydramine 25 mg IV every 8 hours was provided to treat upper airway congestion. The patient reported some pain relief with the first and subsequent doses of diphenhydramine and reported return of pain between doses. Diphenhydramine IV was increased to 50 mg every 4 hours which resulted in mild confusion and sedation. The dose of diphenhydramine IV was reduced to 50 mg every 6 hours, the sedation and confusion improved. She described her pain level as acceptable. The IV diphenhydramine was switched to an oral regimen in the same dose and frequency. The patient obtained satisfactory pain relief without excessive sedation until her death 90 days later.

Their second patient was an 8 year-old boy with recurrent stage IV neuroblastoma with an 8 week history of worsening right upper quadrant abdominal pain and diffuse body pain. Morphine and hydromorphone were given by IV infusion, both caused significant nausea and sedation and neither provided satisfactory analgesia.

Fentanyl IV via patient controlled analgesia (PCA) was titrated to 1100 mcg/hour without adequate analgesia. During a previous admission the patient had received diphenhydramine for pruritis and had reported significant pain relief. Diphenhydramine 25mg IV every 4 hours was begun. He reported good relief of his pain after the first and subsequent IV doses of diphenhydramine. His fentanyl PCA was continued, with no further increases in his cumulative 24 hour dose. Diphenhydramine IV and the fentanyl PCA provided analgesia without excessive sedation until his death 28 days later.

The third case was a 57 year-old man with stage IV non-small cell lung cancer and a four month history of severe left upper extremity pain due to a brachial plexopathy. Sustained release morphine and then transdermal fentanyl caused confusion and provided inadequate analgesia. Further trials of amitriptyline, nortriptyline, and paroxetine were unsuccessful in providing analgesia. He rated his pain as an 8 out of a maximum of 10 while on a methadone PCA. Trials of increased doses of methadone and gabapentin resulted in delirium. He was also receiving dexamethasone 4mg every 8 hours. After oral diphenhydramine 25mg every 6 hours was increased to 50 mg every 4 hours, he rated his pain as only a 1 or 2 out of a maximum of 10. He was discharged home on a combination of oral methadone 20 mg every 8 hours, gabapentin 900 mg three times daily, and

diphenhydramine 50mg every 4 hours while awake. He had adequate analgesia without significant sedation until his death 90 days later.

COMMENT:

Some of the published experimental and clinical data suggest that diphenhydramine may have a role in the management of clinical pain. The successful use of diphenhydramine in our case and the three cases reported by Santiago-Palma and colleagues provide support for another alternative in patients whose pain has failed to respond to opioids and other adjuvant analgesics. A starting dose of 25mg of oral or parenteral diphenhydramine every six to eight hours while awake with titration to effect is supported by the available case reports. Four hundred milligrams daily is the maximum recommended dose of diphenhydramine, according to the pain service at Sloan Kettering Cancer Center. (Santiago-Palama, 2001)

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