



Learning Objectives

1. Explain the relationship between efficacy and drug concentrations for vancomycin.
2. Describe the therapeutic window for vancomycin.
3. Explain the therapeutic drug monitoring controversy for vancomycin.
4. List the criteria for when it is appropriate to measure vancomycin drug concentrations.
5. List optimal drug sampling times for vancomycin if therapeutic drug monitoring is done.
6. Explain the infusion rate of vancomycin necessary to avoid the development of "red man syndrome."

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Clinical/Hospital Pharmacy) and 1992 (Ph.D. Pharmacokinetics). He is on the faculty of 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. His research interests evolve around the use of technology to improve clinical pharmacy activities.

Current Issues Related to Therapeutic Drug Monitoring: Vancomycin

Introduction

Achieving target antibiotic concentrations for vancomycin is a challenge when the patient's status is continuously changing. It is equally challenging for the health care professional to keep up with current monitoring recommendations. There is much discussion about whether or not serum vancomycin levels should be monitored.

Relationship Between Serum Concentration and Efficacy

Many therapeutic ranges for vancomycin have been proposed in the literature. In a study by Andres¹ and coworkers the target peak was 18-30 mg/L measured two hours after a one hour infusion and a trough of 5-10 mg/L. Benkert and colleagues² used a target peak of 20-30 mg/L sampled two hours post infusion and a trough of 5-15 mg/L. Karam³ and colleagues used target concentrations of 30-40 mg/L for a peak and a trough of 5-10 mg/L. Welty⁴ and coworkers dosed vancomycin to maintain a measured peak of 20-25 mg/L and a trough less than 10 mg/L. Unfortunately, none of these or other studies have shown a direct correlation between peak serum concentrations and outcomes desired.⁵

Vancomycin appears to follow concentration dependent killing up to 1.0 mg/L. Above this level it exhibits concentration independent killing.⁶ This means the time above the minimum inhibitory concentration (MIC) is important, not the peak concentration (C_{max}) obtained. The minimum inhibitory concentration for most susceptible organisms is less than 4.0-5.0 mg/L.^{5,6} Most gram positive organisms are susceptible at 0.2-2 mg/L with the exception of methicillin-resistant *Staphylococcus aureus* (MRSA) and *enterococci*. Rather than high C_{max} :MIC ratios, it is more desirable to maintain concentrations 4-5 times the MIC at all times, so trough concentrations should also be kept in the range of 5-10 mg/L.

Two retrospective reviews have related serum trough concentrations to outcome. Zimmermann and colleagues⁷ in a review of 237 patients with infections showed that troughs of more than 10 mg/L reduced fever days and improved white blood cell response but not length of stay or mortality. Mulhern and coworkers⁸ related trough concentration to relapse rates in patients with peritonitis who were treated with continuous ambulatory peritoneal dialysis for end stage renal disease. When the mean predose concentration was less than 12 mg/L, 9 of 14 patients relapsed; when it was more than 12 mg/L, none of the 17 relapsed.

IN THIS ISSUE

5 CE ASSESSMENT QUESTIONS

7 KEY REFERENCES FOR NEW DRUGS

8 NEW FDA APPROVALS

9 PERSPECTIVE FROM AN *IDIS* SUBSCRIBER: DISCONTINUING PROPOXYPHENE (DARVON™) AFTER CHRONIC THERAPEUTIC USE—WHAT ARE THE CLINICAL CONSEQUENCES?

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. Two toxicities associated with vancomycin are believed to be ototoxicity and nephrotoxicity. However, there is some concern about whether these toxicities do occur for vancomycin, at least near the therapeutic range.^{9,10}

Ototoxicity for vancomycin has been reported to occur in less than 2% of the population.⁶ The true incidence has been difficult to determine, because rarely are baseline audiograms done and often vancomycin is used concomitantly with other ototoxic medications. The original ototoxicity report came from Geraci and colleagues.¹¹ They described 6 patients using vancomycin to treat bacterial endocarditis. A patient with renal dysfunction had experienced hearing loss since initiating the vancomycin. This patient's serum vancomycin levels ranged from 80-95 mg/L. From this report, it was determined peak vancomycin levels should be kept below 80 mg/L. Cantu and colleagues⁹ did a literature search to determine if vancomycin was associated with ototoxicity. They found only 53 reported cases over a 30 year period. Of these 53 cases only 17 were patients using monotherapy. The cases found using monotherapy all had reversible hearing loss. Vancomycin levels ranged from 17-62 mg/L, so no specific threshold level was found. There are no controlled studies showing relationships between serum concentrations and ototoxicity. Insufficient evidence exists to show a correlation between ototoxicity and serum levels of vancomycin. Ototoxicity occurs infrequently at a wide range of serum concentrations.

The other reported toxicity associated with vancomycin use is nephrotoxicity. A review by Shalansky⁵ noted most studies from the 1980's forward concluded vancomycin nephrotoxicity is uncommon when not given with another nephrotoxic agent. A frequently quoted retrospective review by Farber and Moellering¹² looked at 98 patients using vancomycin alone. The review found a 5%

Nephrotoxicity and ototoxicity due to vancomycin alone are uncommon,

incidence of nephrotoxicity associated with vancomycin use. However, a 35% incidence of nephrotoxicity was found in patients if an aminoglycoside was used concomitantly. Patients not using other nephrotoxic medications had high trough levels (30-65 mg/L) before a rise in serum creatinine occurred. No levels were available for nephrotoxicity associated with vancomycin and aminoglycoside therapy.¹² As for associating nephrotoxicity with serum levels, again few trials have shown a statistical correlation. Pauly¹³ looked at patients that received aminoglycoside and vancomycin co-therapy. Nephrotoxicity developed in 28 out of 105 patients. Logistic regression showed an association between aminoglycoside trough and vancomycin peak and trough and nephrotoxicity. Two studies, Cimino and colleagues¹⁴ and Rybak and coworkers¹⁵, found a greater risk of nephrotoxicity at trough levels greater than 10 mg/L when vancomycin was used with a nephrotoxic agent. No correlation was found between nephrotoxicity and peak vancomycin levels.⁵ Westrum and coworkers¹⁶ found no association between nephrotoxicity and trough levels. It is not clear whether vancomycin produces the renal

damage, the nephrotoxic agent used concurrently with vancomycin causes it, or whether there is a synergistic effect that results in the renal damage.

Nephrotoxicity and ototoxicity due to vancomycin alone are uncommon, but a correlation may exist between vancomycin use with concomitant known nephrotoxic agents. When considering effectiveness of vancomycin, trough levels need to be greater than the minimum inhibitory concentration. A range of 5-15 mg/L for the trough is deemed effective. Even though it is reported that peaks should be between 20-40 mg/L, there is no evidence supporting improved outcome with these levels. The apparent risk for toxicities (nephrotoxicity or ototoxicity) is not associated with this range, so there does not appear to be a narrow therapeutic window.

When other nephrotoxic agents are used with vancomycin, the therapeutic trough should remain less than 10 mg/L. Based on this, monitoring serum levels should not be necessary unless another nephrotoxic agent is used with the vancomycin, and then it is only necessary to measure a trough.

Dosing Regimens

Multiple approaches to dosing vancomycin exist, including empirical, nomogram, individualized and Bayesian. A small study in patients with normal renal function done by Healey and colleagues¹⁷ found 2 g/day dosing divided as either 1000 mg every 12 hours or 500 mg every 6 hours to be appropriate empiric dosing for patients with normal renal function. Trough levels were drawn and found to be 7.9 to 11.2 mg/L respectively. The 12 hour dosing regimen had less accumulation. In patients with compromised renal function trough levels will exceed these concentrations.⁹ Reviews by Begg and coworkers¹⁸ and Penzak and colleagues¹⁹ of nomograms such as those proposed by Moellering, Matzke, Lake-Peterson and Rodvold, all recommend dosing vancomycin

on a mg/kg basis. In these nomograms, the dosing interval is based on creatinine clearance. Individualized dosing methods based on the approach that Sawchuk and Zaske²⁰ used for aminoglycosides have also been used. This method is based on a one compartment model. Bayesian models require a minimal number of serum samples and can accommodate 1 or 2 compartment models. For the most part, the individualized and Bayesian methods are equally useful at achieving target concentrations.¹⁸ Pyrka²¹ reviewed a variety of dosing methods including empiric algorithms and computer based 1 and 2 compartment Bayesian models. The nomograms with best predictive performance were those by Moellering²² and Lake-Peterson²³.

Karam³ and coworkers found no differences with respect to cure, improvement, failure and nephrotoxicity when patients dosed according to nomogram were compared to patients who were monitored using traditional pharmacokinetic equations. When Welty⁴ and colleagues looked at patients managed through a therapeutic drug monitoring (TDM) service and patients managed empirically, they found that TDM of vancomycin appeared to reduce the incidence of vancomycin related renal insufficiency (TDM 7%, non-TDM 24%). Also, TDM patients received an average of 5 gm less of vancomycin than non-TDM patients. The duration of therapy was an average of 2 days less in the TDM group. Vancomycin doses were adjusted to maintain troughs less than 10 mg/L and peak concentrations 2 hours after a 1 hour infusion of 20-25 mg/L. Benkert and coworkers² evaluated outcomes based on monitoring peak and trough levels versus trough alone. Forty-nine patients were monitored with peak and trough serum vancomycin concentrations. Thirty-seven patients were monitored with

trough level only. Patients in both groups received a mean daily vancomycin dose of about 1500 mg. The mean duration of therapy was not significantly different between the groups. A regression analysis revealed the trough concentration as the only significant factor predicting a change in the dose. The availability of peak concentrations did not increase the number of dose adjustments.

Empiric dosing, nomograms, prospective individualized dosing using traditional pharmacokinetic modeling or Bayesian forecasting all can achieve vancomycin levels that will have successful treatment outcomes. A practitioner should adopt the approach that he/she is most comfortable with and use it consistently.

Infusion Considerations

Infusion of vancomycin can lead to the development of red man syndrome, characterized by one or more of the following: decreased blood pressure, rash, pruritus, urticaria, wheezing and dyspnea.²⁴ These events are thought to be mediated by the release of histamine from mast cells resulting from a chemically induced anaphylactoid reaction – not an antibody associated anaphylactic reaction.^{25,26}

Healy and colleagues²⁷, in a trial conducted in healthy volunteers, examined the effect of 1 and 2 hour continuous infusions of 1000 mg of vancomycin on histamine release and severity of red man syndrome (RMS). Eight out of 10 subjects receiving 1000 mg over 1 hour (17 mg/min) had evidence of RMS. The same 10 subjects also received 1000 mg over 2 hours (8 mg/min). Three out of 10 subjects experienced mild RMS. The 1 hour infusion was also associated with a greater peak and total release of histamine than the 2 hour infusion. This study demonstrated that administration of vancomycin

over 2 hours reduced the frequency and severity of RMS.

Polk and colleagues²⁸ studied two infusion regimens for vancomycin in 11 healthy volunteers. The doses were 500 mg and 1000 mg, both infused over 1 hour. Nine of the subjects receiving 1000 mg (17 mg/min) experienced RMS. None of the same 11 subjects receiving 500 mg over 1 hour (8 mg/min) experienced RMS. The authors acknowledged that the 9 subjects receiving the 17 mg/min infusion that developed the reactions would have probably gone un-noticed in a clinical setting. None exhibited pruritus or angioedema.

...all can achieve vancomycin levels that will have successful treatment outcomes.

Krogstad and coworkers²⁹ reported 4 subjects who received vancomycin infusions. Two subjects were given 500 mg over a 30 minute infusion (17 mg/min) and they experienced no objective or subjective side effects. These results conflict with those above, but this study had a small sample size. Two different subjects received 1000 mg over a 30 minute infusion (33 mg/min) and both experienced RMS. One subject's reaction was so severe that the infusion was stopped at 21 minutes with a total dosage of 700 mg. The patient stabilized after 10 minutes. These studies, show that the rate of infusion influences side effect frequency and severity.

Wallace and coworkers³⁰, investigated RMS prophylaxis. Thirty-three subjects were followed during their first two doses of vancomycin (1000 mg over 1 hour). Before their first dose they were randomized to receive either 50 mg diphenhydramine or placebo 45-

60 minutes before the vancomycin infusion. Of the 17 patients with placebo treatment, 8 or 47% had RMS.

...the length of infusion should be calculated such that the infusion rate does not exceed 10 mg/min.

None of the 16 pre-treated with diphenhydramine had a first dose reaction. Renz and coworkers²⁶, in 40 patients undergoing elective arthroplasty, found that pretreatment with H₁ and H₂ blockers allowed 89% of their patients to receive 1000 mg of vancomycin at an infusion rate of 100 mg/min. They confirmed that rapid infusions of vancomycin can be safely given if the patient is pre-treated with antihistamines and that, if the flushing reaction occurs, there are not major cardiovascular effects.

Many of the studies investigating the development of RMS have been conducted in healthy volunteers. Stier and coworkers³¹ reported the development of this phenomenon in critically ill patients. They prospectively studied 16 critically ill patients after open heart surgery. They infused 1000 mg vancomycin over 30 minutes without any adverse hemodynamic changes. All patients received H₂ blockers. One patient did develop the red flushing but this was not associated with any change in cardiac output, heart rate, blood pressure or systemic vascular resistance. This study is consistent with others in that there is rarely a change in hemodynamics in the patients that do develop the syndrome. Prior to 1990 there was a report that H₂ blockers alone had no effect on anaphylactoid

reactions, but the recent work by Renz and coworkers^{25,26} might be shedding a different light on this.

Begg¹⁸ reports that it is generally accepted that vancomycin should be administered by slow infusion over at least 1 hour. However, based on the above studies, it is appropriate to develop a policy that for doses of vancomycin that are less than or equal to 1250 mg, vancomycin should be infused over 90 minutes. For doses that are greater than 1250 mg, the length of infusion should be calculated such that the infusion rate does not exceed 10 mg/min.

Sampling Recommendations

Drug levels that are utilized to make pharmacokinetic dosage adjustments must be correctly and accurately obtained.³² Failure to do so can result in dangerous and inappropriate adjustments in drug therapy.

Justification for monitoring peak concentration measurements with vancomycin is lacking. However, if vancomycin peak concentrations are obtained, there are several things that must be remembered. Vancomycin pharmacokinetics is described by 1, 2 and 3 compartment models.³³ To get accurate serum levels to base pharmacokinetic predictions upon, one must be certain the distribution phase is complete before the peak serum level is drawn. If not, the elimination half life will be underestimated. This has led to inconsistencies in the timing of peak concentrations related to the distribution phase⁵. There are many suggested times to obtain peak values ranging from 15 minutes to 2 hours post infusion^{1,33-35}. A summary table by Melamed and colleagues³⁶ recommends taking a peak 1 hour post infusion. Many studies have taken the peak levels 2 hours following an infusion.

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. Populations that may require close monitoring 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 ototoxic medications (like

amphotericin B, furosemide, ethacrynic acid, or aminoglycosides), patients with rapidly changing renal function, malignancy, obesity and intensive care situations.^{18,21} It is important to monitor serum creatinine concentrations as a marker for potential nephrotoxicity, although the drug levels may rise before the serum creatinine does.²¹

Conclusion

There is no strong evidence to relate peak vancomycin levels with toxicity or efficacy. On the other hand, trough levels need to be above the minimum inhibitory concentration to be effective and there is some evidence that shows better outcomes with troughs that are in the range of 10-15 mg/L. There is limited evidence to show that when troughs are above 10 mg/L there is a slightly greater chance for toxicity when the patient is also on another nephrotoxic agent. Therefore, there is no therapeutic window for vancomycin and it is not recommended that therapeutic drug monitoring using peaks and troughs be done. It would be advisable, however, to monitor steady state trough concentrations to ensure that adequate trough levels are being achieved and to try to avoid nephrotoxicity if the patient is on another nephrotoxic agent. Those troughs should be obtained immediately before a dose, preferably the fifth dose, to ensure that steady state has been reached. Vancomycin infusion should be slow in order to

minimize the chance of developing a histamine reaction. Doses less than or equal to 1250 mg should be infused over 90 minutes, and doses greater than this should not exceed an administration rate of 10 mg/min.

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(continued on page 6)



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 020-000-02-027-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, 2004 to receive credit.

CE REGISTRATION

TITLE OF EDUCATIONAL ACTIVITY (ARTICLE)

020-000-02-027-H01

CURRENT ISSUES RELATED TO THERAPEUTIC

ACPE # DRUG MONITORING: VANCOMYCIN

NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

SOCIAL SECURITY NUMBER _____

PHARMACY LICENSE NUMBER(S) _____

I HEREBY CERTIFY THAT I HAVE TAKEN THIS TEST:

Signature/Date

(circle the correct answer)

1. The success of vancomycin therapy is related to:

- a. Maintaining concentrations 4-5 times the MIC at all times.
- b. Having the C_{max} concentration 4-5 times the MIC.
- c. Keeping peaks below 40 mg/L.
- d. Maintaining an average steady state concentration of 25 mg/L.

2. Which one of the following concentration efficacy statements is not true?

- a. No studies have shown a correlation between peak serum concentration and desired outcome.
- b. Maintaining troughs above 10 mg/L has been associated with some outcome measurements (reduced fever days and white cell counts) but not length of stay or mortality.
- c. Troughs greater than 12 mg/L have resulted in fewer relapses of peritonitis infections.
- d. Concentration-dependent killing does not occur if trough concentrations are not maintained above 10 mg/L.

3. Which statement is true regarding vancomycin and ototoxicity?

- a. Hearing damage is fairly common when vancomycin is used alone.
- b. When vancomycin is used alone, the hearing damage is usually irreversible.

- c. There is a clear relationship between ototoxicity and serum levels above 50 mg/L.
- d. It occurs infrequently, at a wide range of levels.

4. Which statement is true regarding vancomycin and nephrotoxicity?

- a. Renal damage is fairly common when vancomycin is used alone.
- b. Although evidence is conflicting, there is no strong association between peak levels and nephrotoxicity.
- c. There is no evidence to support using trough levels to monitor for nephrotoxicity.
- d. Concurrent use of an aminoglycoside with vancomycin decreases the risk of toxicity.

5. Which statement is not correct about vancomycin serum levels?

- a. Peak levels are not associated with efficacy or toxicity.
- b. Trough levels should be maintained above the MIC to ensure efficacy.
- c. Elevated trough levels are associated with nephrotoxicity when a nephrotoxic agent is also present.
- d. It is not necessary to measure peak or trough vancomycin levels.

6. Which dosing approach has clearly been shown to be more effective when initiating therapy?

- a. Empiric dosing.
- b. Nomograms based on weight and/or renal functions.
- c. Traditional or Bayesian computer programs.
- d. All have been effective, none has a clear advantage.

7. The most valuable marker to adjust vancomycin dose is:

- a. Measured creatinine clearance.
- b. Trough concentration, measured within 30 minutes of the next dose.
- c. Peak concentration, 60 minutes after infusion stops.
- d. Peak concentration 120 minutes after the infusion stops.

8. Which one of the following patients will not require intensive monitoring of vancomycin trough levels?

- a. A patient with gram-positive peritonitis.
- b. A patient on hemodialysis awaiting renal transplant.
- c. A patient with severe septicemia also on gentamicin.
- d. A motor vehicle accident victim in the intensive care unit with extensive road burn.

9. Red man syndrome with vancomycin use is:

- a. An antibody associated anaphylactic reaction.
- b. A chemically induced anaphylactoid reaction.
- c. Not blocked by the use of antihistamines.
- d. Not related to the rate of administration.

10. If peak and trough vancomycin levels are measured in a patient with rapidly changing renal function, which statement is not true regarding these samples?

- a. The peak and trough can be measured around a dose, if steady state has been reached.
- b. Steady state is usually achieved around the 5th dose.
- c. A peak measured right after the infusion stops is best for pharmacokinetic calculations.
- d. A peak measured 2 hours after the infusion stops is acceptable.

PROGRAM EVALUATION

	Excellent				Poor	
	5	4	3	2	1	
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.						

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QUICK GUIDE

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FDA APPROVAL PACKAGES

SUMMARY AND ANALYSIS OF PIVOTAL CLINICAL DRUG TRIALS, PHARMACOLOGY, TOXICOLOGY AND PHARMACEUTICAL INFORMATION IN ONE COMPREHENSIVE DOCUMENT
PIVOTAL STUDIES WITHIN APPROVAL PACKAGES IDENTIFIED AND ABSTRACTED
ORGANIZED INTO STANDARD FORMAT WITH TABLE OF CONTENTS
RAPID RESPONSE TO ALL REQUESTS

DRUG VOCABULARY AND THESAURUS

COMPREHENSIVE CONTROLLED VOCABULARY OF PROPRIETARY AND NON-PROPRIETARY NAMES
US AND INTERNATIONAL DRUG SYNONYMS CROSS-REFERENCED
OVER 8,000 GENERIC TERMS
OVER 21,800 DRUG TERMS
CONTINUALLY UPDATED
UNIQUE NUMERIC INDICATOR FOR EACH DRUG

CUSTOMIZED DRUG INFORMATION INSTRUCTION

BASIC OR ADVANCED INSTRUCTION IN DRUG INFORMATION AND INFORMATICS FOR PRACTICING PHARMACISTS
PROGRAM FACULTY INCLUDE MEMBERS OF THE UNIVERSITY OF IOWA COLLEGE OF PHARMACY
UNIVERSITY AND COMMUNITY HOSPITAL EXPERIENCES AVAILABLE

PHARMACEUTICAL INFORMATION RETRIEVAL AND EVALUATION SERVICE SPECIALIZING IN:

DRUG INFORMATION
CLINICAL PHARMACEUTICS
FORMULARY REVIEWS
MEDICAL-LEGAL QUESTIONS

COMMITTED TO:

RAPID RESPONSE
EVIDENCE BASED EVALUATION

New Drugs: Key References

This new drug bibliography provides a selection of key clinical studies and reviews of new drugs approved by the FDA November 2002 through January 2003. An *IDIS* search retrieved articles relevant to the new drugs and their approved uses.

Adalimumab

Weinblatt ME, Keystone EC, Furst DE, Moreland LW, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003;48:35-45. (FDA pivotal study, *IDIS* Article Number 492001)

Adalimumab was found to be safe and effective, in doses of 20, 40 or 80 mg given subcutaneously every other week, in conjunction with methotrexate during a 24-week, double-blind randomized trial of 271 patients.

Alefacept

Krueger GG, Papp KA, Stough DB, Loven KH, et al. A randomized, double-blind, placebo-controlled Phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2002; 47:821-833. (FDA pivotal study, *IDIS* Article Number 490925) **Durable clinical improvement was evaluated in this double-blind, randomized, controlled trial of 553 patients using alefacept in once a week, 7.5 mg injections during two 12-week study periods.**

Ellis CN, Krueger GG, Bennett D, Haney J, et al. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med* 2001; 345:248-255. (*IDIS* Article Number 467244) **Efficacy of alefacept was evaluated in a multi-center, randomized, placebo-controlled trial of 229 patients with chronic plaque psoriasis who received intravenous doses of alefacept 0.025, 0.075 or 0.150 mg per kilogram of body weight or placebo.**

Atomoxetine

Spencer T, Heiligenstein JH, Biederman J, Faries DE, et al. Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2002; 63:1140-1147. (*IDIS* Article Number 491627) **Two double-blind, stratified, randomized controlled trials of 291 pediatric patients who met DSM-IV criteria for attention deficit/**

hyperactivity disorder evaluated efficacy of atomoxetine compared with methylphenidate or placebo.

Eletriptan

Goadsby PJ, Ferrari MD, Olesen J, Stovner LJ, et al. Eletriptan in acute migraine: A double-blind, placebo-controlled comparison to sumatriptan. *Neurology* 2000;54:156-163. (*IDIS* Article Number 441229) **This randomized, double-blind, controlled trial evaluated safety, efficacy and tolerability of eletriptan in oral doses of 20, 40 or 80 mg compared with 100 mg oral doses of sumatriptan or placebo in 857 patients diagnosed with migraine.**

Milton KA, Scott NR, Allen MJ, Abel S, et al. Pharmacokinetics, pharmacodynamics, and safety of the 5-HT_{1B/1D} agonist eletriptan following intravenous and oral administration. *J Clin Pharmacol* 2002; 42:528-539. (*IDIS* Article Number 480734) **A placebo-controlled, double and single blind, randomized crossover study assessed the pharmacokinetics, pharmacodynamics and safety of oral and intravenous doses of eletriptan in 55 healthy male subjects.**

Icodextrin

Plum J, Gentile S, Verger C, Brunkhorst R, et al. Efficacy and safety of a 7.5% icodextrin peritoneal dialysis solution in patients treated with automated peritoneal dialysis. *Am J Kidney Dis* 2002; 39:862-871. (*IDIS* Article Number 480865) **This randomized, multi-center trial compared the safety, efficacy and metabolic effects of icodextrin 7.5% solution with glucose 2.27% solution for automated peritoneal dialysis in 39 patients over a 12-week period.**

Nitazoxanide

Amadi B, Mwlya M, Musuku J, Watuka A, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomized controlled trial. *Lancet* 2002; 360:1375-1380. (FDA pivotal study, *IDIS* Article Number 488791) **In this randomized, placebo-controlled trial, nitazoxanide was given in 100 mg daily oral doses for three days to 50 HIV-seropositive and 50 HIV-seronegative children suffering from cryptosporidial diarrhea.**



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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
Adalimumab (BIOL) <i>Humira</i>	Abbott Laboratories (Dec. 31)	ANTI-TNF MONOCLONAL AB 82000419 (4 citations)	Moderate to severe active rheumatoid arthritis, used alone or with methotrexate or other DMARD.	Arthritis, Rheumatoid 714.0
Alefacept (BIOL) <i>Ameviva</i>	Biogen, Inc. (Jan. 30)	ALEFACEPT 14000039 (18 citations)	Treatment of adults with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.	Psoriasis & Pityriasis NEC 696.
Atomoxetine (1S)*** <i>Strattera</i>	Lilly (Nov. 26)	ATOMOXETINE 28160422 (20 citations)	Non-stimulant, selective norepinephrine reuptake inhibitor for the treatment of Attention Deficit/Hyperactivity Disorder in children, adolescents and adults.	Syn-Hyperkinetic, Childhood 314.
Eletriptan Hydrobromide (1S)*** <i>Relpax</i>	Pfizer (Dec. 26)	ELETRIPTAN 28081295 (47 citations)	Acute treatment of migraine.	Migraine 346.
Icodextrin (1S)*** <i>Extraneal</i>	Baxter Healthcare (Dec. 20)	ICODEXTRIN 40360001 (10 citations)	Osmotic agent for use in peritoneal dialysis.	Dialysis, Peritoneal 54.98
Nitazoxanide (1P)***** <i>Alinia</i>	Romark (Nov. 22)	NITAZOXANIDE 8040012 (24 citations)	Antiprotozoal agent for the treatment of diarrhea caused by cryptosporidium and giardia lamblia in pediatric patients one to eleven years old.	Cryptosporidiosis 007.4 Giardiasis 007.1

* Through January 2003 Update. Complete bibliographic citations will be provided upon request.

** Not applicable.

*** New molecular entity given standard review by FDA.

**** Designated orphan drug.

***** New molecular entity given priority review.

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

Discontinuing propoxyphene (Darvon™) after chronic therapeutic use – what are the clinical consequences?

Perspective from an



IDIS Subscriber

Because of renewed safety concerns with the use of daily therapeutic propoxyphene doses combined with the social use of alcohol or therapeutic use of other sedatives (See *World of Drug Information*, 2001, Volume 12, Issue 4), patients who have used propoxyphene daily, from a few months to many years, will be faced with propoxyphene discontinuation.

Propoxyphene has a chemical structure closely related to methadone and the pharmacokinetics of propoxyphene and its major metabolite closely resemble the pharmacokinetics of methadone. However, a variability in individual rates of propoxyphene clearance is reported.¹

Propoxyphene was first marketed in the United States as an analgesic in 1957. It was promoted by Eli Lilly Company as a non-narcotic analgesic equal in potency to codeine, but without addiction or abuse potential. Effective marketing by Eli Lilly combined with the physician's need for an intermediate analgesic product with a potency between aspirin or acetaminophen and opioids led to the widespread use of propoxyphene.

Published reports of propoxyphene dependence include experiments conducted in the 1960's and case reports of dependence associated with therapeutic or illicit use. Chernish and Gruber¹ gave propoxyphene 65mg four times daily for six months to twelve subjects under double blind conditions and then administered

the opioid antagonist nalorphene 3mg IM. No physical evidence of withdrawal was observed in any subject. Cass and colleagues² conducted a similar study in 19 subjects given propoxyphene 65mg four times daily for three months and then abruptly withdrawn. Three of the patients developed minor abstinence symptoms including diarrhea and nausea. Fraser and Isbell,³ at NIMH Addiction Research Center, studied high dose propoxyphene in five former addicts. They increased propoxyphene doses over 15 days to a maximum daily dose of 825mg and maintained that dose for 53 or 54 days before abruptly discontinuing the propoxyphene. All the subjects had subjective complaints and objective signs of physical abstinence including yawning and perspiration.

Over time the belief became established that only patients with prior psychiatric or drug abuse histories could become physically dependent on propoxyphene. Published case reports do not support that belief.

In a recent review of the clinical perspective of opioid tolerance, Collett⁴ emphasized that,

“Neither the prevalence nor the pattern of opioid withdrawal has been systematically studied in patients with pain. In the clinical setting, the lowest dose and shortest duration of treatment [with an opioid] that may predispose to a significant

abstinence syndrome is not known.”

Collett cites early surveys of addicts undergoing treatment in the 1920's and 1930's that reported 9% and 4% of addicts respectively began their opioid use with a medical prescription for pain.

Between 1969 and 1971 the nonmedical and intravenous abuse of propoxyphene had emerged as a serious problem among US Army soldiers stationed in West Germany.⁵ Rapid tolerance to IV propoxyphene was described by seven addicts, four of whom had used heroin in the past. Their daily IV propoxyphene dose ranged from 780 to 2340mg in 4-6 separate injections. All seven experienced mild opioid abstinence symptoms on propoxyphene withdrawal.

Case reports – propoxyphene withdrawal after medical use

Almost thirty years ago Maletzky,⁶ an Army psychiatrist at Ft. Rucker, AL, published a case series of seven patients without prior psychiatric or drug abuse histories who became dependent on propoxyphene after usual medical use and who demonstrated clear signs of opioid withdrawal when propoxyphene was discontinued. He was concerned that the potential for development of physical

tolerance in nonpsychiatric propoxyphene patients was greater than previously suspected. He referenced several other published case reports and provided clinical details for seven cases from his practice. One of his patients provided the following history: A 52 year-old male, took his wife's propoxyphene for back sprain. Over the next two years he took it for minor pains, then noticed that he needed it almost daily. He abruptly stopped the propoxyphene and experienced agitation, nausea and tremors. He tried several times to stop the drug over the next two years without success. Eighteen hours after stopping the drug (2600mg/daily from forty 65mg doses) he was extremely agitated and diaphoretic. He was hospitalized and withdrawn at a rate of 130mg every other day without incident. There was no history of psychiatric consultation or other drug abuse. Eighteen months after withdrawal he still experienced occasional craving for propoxyphene.

Another patient provided the following history: A 32 year-old male was given propoxyphene for pain secondary to a fractured femur from an auto accident. He was discharged on propoxyphene and found that when he decreased the daily dose to less than four capsules his pain returned. Over a period of several months the pain returned even when taking four capsules daily. He increased his daily dose over the next several years to treat his pain.

EDITORS NOTE:

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

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Eventually he was suspected of heroin abuse and hospitalized and treated with methadone 40mg/day. He then revealed his history of escalating propoxyphene use. Methadone was gradually tapered and at one year follow up he had not used propoxyphene. There was no prior history of psychiatric consultation or other drug abuse.

Collins and Keifer⁷ published a case of propoxyphene dependence developing over 15 years of medically supervised use. A 23 year-old female started on propoxyphene at age 8 for "headaches and leg cramps" of unknown cause. Over the years her daily propoxyphene use gradually increased as each successive dose failed to prevent the return of headaches and generalized body aches. Eventually her daily dose was increased to 2,600mg (40 capsules). Two weeks before admission to hospital she had attempted abrupt withdrawal from propoxyphene. She experienced extreme agitation, insomnia, muscle cramping, tremulousness, dizziness and worsened headaches. Detoxification was begun at a dose of 8 capsules daily. Insomnia, anorexia, worsened headaches, muscle tension and mild tremor occurred. Each time the propoxyphene dose was decreased the patient became markedly anxious. The drug was withdrawn over a 10 day period. She was hospitalized for 21 days, by the last week her sleep pattern and appetite had almost returned to normal, she gained 10 pounds during her admission.

Hedenmalm⁸ published a case of secret propoxyphene use which complicated a patient's post surgical course. A 69 year-old female had been taking propoxyphene napsalate 1-2 tablets as needed for a chronic pain syndrome. On the third day after hip surgery (nothing by mouth for 2.5 days) she became increasingly confused, hallucinated and had severe sweating. She became unable to respond and had uncontrolled kicking movements. Despite being given a phenothiazine and a butyphenone during the night she did not improve. In the morning she was given 100mg of propoxyphene and improved and

when given another 100mg became calm. She was given propoxyphene 400mg daily plus 100-200mg as needed. On day 7 her propoxyphene dose was reduced by 50mg every other day. Her condition worsened, by day 13 she was returned to the Intensive Care Unit. She was stuporous, had dilated pupils, a temperature of 42.3 C, a pulse of 130-140, and blood pressure down from 180/75 to 80/50mmHg. She was placed on a morphine infusion and improved gradually. On day 16 propoxyphene was reintroduced at a dose of 900-1000mg daily. Her propoxyphene dose was reduced by 100mg each week. No further withdrawal symptoms occurred. After nine weeks she no longer received propoxyphene. She eventually revealed that she had taken 1-3 grams of propoxyphene daily for at least one year.

Case reports – propoxyphene withdrawal after non- medical use

Wolfe and Reidenberg¹⁵ published the case of a young woman who was introduced to propoxyphene after gynecologic surgery. After a brief period off propoxyphene she restarted the drug and was able to perform her household and social duties. When she was off the drug she would feel depressed and distant from her husband and children. If drug intake was interrupted, she experienced a generalized aching sensation, watery diarrhea 2-3 times daily, sweating of forehead and hands and rhinitis. When her pharmacy closed and a period off the drug was extended she noticed nausea, vomiting and nasal stuffiness in addition to the previously described syndrome. Eventually she increased her propoxyphene intake to 13 capsules 2 or 3 times a day to "make me high." She had tried methadone prescribed for her propoxyphene dependence and noted that 3 methadone 5mg tabs gave her the same reaction as 8 propoxyphene capsules. Eventually she was admitted to the hospital for treatment of her propoxyphene dependence. When admitted she was placed on 20 capsules of propoxyphene in divided doses daily. Forty-eight hours after transfer to the research center, the propoxyphene was

replaced with identical placebo capsules given in the regimen of 20 capsules in divided doses. Fifteen hours after the placebo had been substituted, the patient began to complain of aching all over. Over the next 8-12 hours she developed rhinitis, anorexia, and marked tiredness. She began to complain of "catching the flu," was quite irritable, and wanted to be left alone. During the second 24 hours of abstinence from propoxyphene she experienced episodes of vomiting, nightmares, and irritability with insomnia and intermittent sleep. After 48 hours, real propoxyphene was substituted in the same regimen of 20 capsules daily in divided doses. Within 12 hours of receiving the first dose of real propoxyphene she felt much better, and within 24 hours of receiving the first dose of the drug she was asymptomatic. The dose of propoxyphene was gradually tapered until she was off the drug and remained asymptomatic. Several times during the reductions of her dose she experienced some irritability and rhinitis for a day or two after the dose reduction.

Detoxification from propoxyphene

D'Abadie and Lenton⁹ describe the detoxification of six patients, who they describe as typical, using +/- 3000 mg propoxyphene/day plus other drugs. They determined the initial daily dose of propoxyphene from the patient's history. That dose is given on the first day in four equally divided doses. Then the total daily propoxyphene dose is reduced by approximately 10% daily until the drug is withdrawn. In their experience detoxification is often associated with significant anxiety and agitation, in the absence of objective signs of withdrawal.

Maletzky⁶ describes detoxification of seven patients with no drug abuse or psychiatric history who were taking between 1560 and 2600mg of propoxyphene daily. The starting propoxyphene dose for the tapering regimen was the patient's current daily dose (not necessarily the prescribed daily

dose). He reduced the propoxyphene dose by 130mg every other day usually without incident. All his patients were in-patients during the detoxification regimen.

Fishbain and colleagues¹⁰ have described various opioid detoxification protocols including methadone substitution, codeine or other opioid substitution, opioid of choice and protocols, using various other medications.

Detoxification from methadone

It is repeated throughout the published work on opioid withdrawal that many addicts prefer heroin over methadone withdrawal. The stated reason is they would rather get the acute withdrawal syndrome over within 7-10 days followed by a few weeks of insomnia, nervousness, and muscle aches and pain than experience the severe generalized pain and insomnia associated with methadone withdrawal.

Lipkowitz and colleagues¹¹ described the abrupt withdrawal of high dose methadone (80-180mg/day) in four addicts. Three of the four cases complained of severe symptoms of generalized pain and insomnia, without objective evidence or their complaints. The fourth case, whose methadone dose had been tapered to 20mg daily, complained of sweating, restlessness, sleeplessness, abdominal cramps and increased lacrimation which began two days after methadone was withdrawn.

Senay and colleagues¹² studied withdrawal from methadone in 127 successfully maintained patients. The daily methadone maintenance doses ranged from 6 to 80mg at the start of the withdrawal study. Almost 75% of the group's daily methadone

dose was between 15 and 39mg. One open label and one blinded group continued their daily maintenance dose. In the open label group 88% and in the blinded group 71% completed the study period without interruption. In the rapid withdrawal group (10 percentage points/week) 15% and in the gradual withdrawal group (3 percentage points/ week) 53% completed the study period without interruption. Symptoms reported in the highest frequency by the various groups during the study period appear in Table 1.

They concluded that withdrawal from methadone maintenance should utilize a dose reduction schedule of approximately 3 percentage points weekly. They

any event the residual symptoms can take some time to resolve. Previous work by Gossop had demonstrated that methadone withdrawal led to a prolonged withdrawal syndrome, with patients reporting moderate discomfort 10 days after their last methadone dose. Subsequent work confirmed that patients were still reporting more symptoms than controls 14 days after the discontinuation of methadone. The withdrawal syndrome was assessed by having each patient complete a 20-item version of the Opiate Withdrawal Scale each day during the study. Each item was rated as: none, 0; mild, 1; moderate, 2; severe, 3. The 20 items were: feeling sick, diarrhea, stomach cramps, stiffness of arms and legs, spontaneous twitching,

In a later report, Gossop and Strang¹⁴ studied 83 physically dependent patients with histories of heroin or methadone use who were withdrawn over 10 days using methadone. In their experience, many addicts believed withdrawal from methadone was more severe than withdrawal from heroin. Bone pain and muscular aches were prominent symptoms attributed to methadone withdrawal by addicts. Many of the addicts claim to prefer abrupt withdrawal from heroin to any methadone detoxification scheme. They found no difference in the onset or decay of withdrawal symptoms between the two groups, but the severity of withdrawal symptoms in the methadone group was greater both early and late during the 23 day withdrawal period. The most severe symptoms reported in the methadone group included: coldness, muscular tension, aches and pains, weakness and insomnia. Their results do not support the previous belief that withdrawal from methadone is less severe than withdrawal from heroin.

Table 1. Symptoms that Significantly Differentiate Treatment Groups by Weekly Rate of Occurrence

Symptom	Known Maintenance	Blind Maintenance	Rapid Withdrawal	Gradual Withdrawal
Irritability			+	
Perspiration				+
Constipation		+		
Anorexia			+	
Lack of energy			+	
Lacrimation			+	+
Aching bones				+
Depressed			+	
Backache		+		
Headaches			+	
Increased frequency of urination			+	

+ Highest Frequency

Table modified from Senay EC, et al. Arch Gen Psychiatry 1977;34:361-7.

believed larger dose decrements would be associated with increased dropout rates and subjective distress. Their results were consistent with the belief that withdrawal from methadone could be associated with a clinically significant protracted abstinence syndrome.

Gossop and colleagues¹³ studied 132 opiate addicts using a 10 or 21 day methadone withdrawal procedure. They believe the widespread acceptance of methadone as a withdrawal drug may have diverted attention from some of the problems associated with methadone withdrawal. Some have likened the methadone withdrawal syndrome to a case of influenza, others have reported the syndrome to be subjectively severe, but objectively mild. In

trembling hands, feelings of coldness, gooseflesh, hot and cold flushes, increased sweating, runny nose, heart pounding, fatigue or tiredness, muscular tensions, aches and pains, weakness, yawning, sneezing, runny eyes and insomnia. The group who was withdrawn over 10 days reported a withdrawal syndrome that began to increase in severity after 3 days, reaching peak intensity after 13 days with a subsequent gradual decline. In the 21 day group, withdrawal symptoms began around day 10 and peaked on day 20, and then declined. In both groups methadone withdrawal symptoms were most severe near the end of the gradual methadone reduction. In the 21 day group, the withdrawal syndrome was more protracted, with patients not fully recovered until 40 days after the beginning of withdrawal.

Comment

In the absence of clinical trials of propoxyphene withdrawal after chronic use or consensus expert opinion or guidelines on propoxyphene withdrawal it is not possible to offer either general or patient specific procedures for propoxyphene withdrawal. However, after review of the published cases of propoxyphene or methadone withdrawal and the reports of attempted detoxification from propoxyphene or methadone, the reader should be aware of the range of withdrawal symptoms reported and several approaches for tapering propoxyphene.

Which patients will experience propoxyphene withdrawal syndrome?

Although the limited data after short term propoxyphene use in routine doses did not describe a propoxyphene withdrawal syndrome on abrupt withdrawal, we might suspect a withdrawal syndrome would be common after withdrawal from chronic use.

If the patient has never interrupted propoxyphene therapy even for a few days or a week, or cannot provide any history of the syndrome that occurred when propoxyphene was stopped, there is no basis to speculate on whether or not a withdrawal syndrome might occur in that patient. On the other hand, if the patient describes a new or worsening syndrome (generalized pain, muscle aches, bone pain, or worsening insomnia without explanation) that was relieved by increasing his or her daily propoxyphene dose, such a history is consistent with the possibility of a prior unrecognized propoxyphene withdrawal syndrome. If the syndrome has occurred on multiple occasions when propoxyphene therapy was interrupted and could be treated by successive increases in the propoxyphene dose, the probability of a similar

syndrome or withdrawal is increased.

What drug(s) can be substituted for propoxyphene?

A sufficient dose of any mu agonist opioid will immediately relieve a propoxyphene withdrawal syndrome. It would be wise to avoid any of the partial mu agonists such as nalbuphine (Nubain[®]), butorphanol (Stadol[®]), or pentazocine (Talwin[®]-NX[®]) as they could worsen propoxyphene withdrawal.

Several other drugs which are not cross tolerant with propoxyphene would not prevent withdrawal but may be useful in treating various pain syndromes including acetaminophen, tramadol (Ultram[®]), and non-steroidal anti-inflammatory drugs.

What about tapering the propoxyphene dose?

Several examples of successful regimens for tapering propoxyphene after chronic use were described in the case reports. Some type of tapering regimen would almost certainly be preferable to the abrupt discontinuation of chronic propoxyphene use.

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