



Safe Administration of Intravenous Immune Globulin (IVIG)

Objectives

1. Explain the important considerations for the preparation of IVIG for administration.
2. Discuss the role of infusion pumps and in-line filters for the administration of IVIG.
3. Describe the factors that influence the rate of administration of IVIG.
4. Understand and explain the special considerations for the administration of IVIG including during renal failure, the dose for obese patients and premedications to avoid complications.

Introduction

Intravenous immune globulin (IVIG) has been available for use in the United States since 1984. The use of IVIG nearly tripled from 6.6 million grams in 1990 to 16.5 million grams in 1996. Manufacturers were able to keep up with demands up until that point. However, the ensuing years resulted in shortages as demands exceeded the manufacturers'

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ability to supply the product. In 2000 it was reported that the demand for IVIG was growing by 9% annually.¹ With the cost of IVIG at approximately \$100 per gram², a typical treatment for a patient is about \$2000 - \$6000 per day. Chen³ and colleagues looked at the use of IVIG in 107 patients and found that 43% received it for an FDA approved use, 52% received it for an unlabeled use and 5% received it for unspecified reasons. It is not surprising that there is significant interest by medical professionals, the public and those institutions that are paying for the administration of this drug that it be used wisely. This paper will not address appropriate indications of IVIG, but instead will focus on making sure that once it has been determined to use IVIG, that it is prepared and administered in a safe manner.

IVIG Preparation for Administration

IVIG preparations generally consist of concentrated immunoglobulins (Ig), principally IgG, with a distribution of other immunoglobulins that roughly reflects that in normal human serum.⁴ These immunoglobulins come from a large number of human donors. Cohn-Oncley ethanol fractionation is used as an initial step in the preparation of pooled immunoglobulin. Different

manufacturers use different steps for the subsequent purification processes. These procedures remove protein contaminants, minimize the concentration of IgG aggregates, and deactivate viral contaminants such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV).⁵ All donor serum samples are screened for antibodies to HIV, HCV, hepatitis B surface antigen and elevated levels of alanine aminotransferase (ALT). Following an outbreak of HCV in 1994 the FDA increased the requirements for monitoring pooled serum that is used to prepare IVIG products.^{6,7} Different processes of purification necessitate different procedures to reconstitute or prepare IVIG for administration. It is important that the pharmacist or nurse who prepares the IVIG for administration follow the manufacturer's instructions.

Reconstitution of IVIG must be done using the diluents provided by or specified by the manufacturer. Vials should be warmed to room temperature before reconstitution. Dissolution of IVIG can take from 5 to 30

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minutes. Vials should be swirled gently during reconstitution; shaking can cause excess foaming.⁸ If reconstitution is done in a laminar flow hood and the product refrigerated, the product can be kept for 24 hours before administration; otherwise it should be administered within 2 hours of preparation. Filters can be used during the reconstitution process, but they must be 15 microns or larger. The final IVIG preparations should be visually inspected prior to administration to ensure that there is no particulate matter or discoloration.

Administration Devices and Filters

IVIG preparations should be administered via separate tubing.⁹ The only two compatibilities that have been evaluated are the use of fluconazole or sargramostim with IVIG. They can be administered together through a Y-site.¹⁰ No other medications have been evaluated, so it is not recommended that IVIG be infused concurrently with any other medications.¹¹ There is no consensus about the use of inline filters for human immune globulin. Several manufacturers recommend that filters be used with their product, so it would be important to follow the manufacturer's recommendation for the particular preparation being used.

Lemm¹² reviewed the differences in the composition of various commercial IVIG preparations. He reported that some IVIG products have higher sucrose and sorbitol content than others and consequently a higher osmolality and tend to be more viscous. High osmolality and high sugar content IVIG preparations are not tolerated well when administered too rapidly and can result in declining renal function. The FDA's Center for Biologics Evaluation and Research (CBER)¹³ issued a warning about acute renal failure and administration of IVIG. This letter encouraged physicians to ensure that patients were adequately hydrated, and also warned that some patient groups may be at risk for acute renal failure (patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia and anyone who may be on concomitant nephrotoxic drugs). CBER insisted that the manufacturer's recommended dose not be exceeded and that if dose, concentration or rate of administration could be reduced, there would be a reduced chance of developing acute renal failure. No publication has addressed the merits of administering IVIG by a pump versus gravity fed administration sets. However, because of the increased viscosity due to the higher sugar content these products

would not readily flow through gravity lines. In light of the recommendation that the rate of administration be lowered and monitored closely for those products it would be a definite advantage to use pump administration for more accurate control.

Rate of Administration

It is clear that the osmolality and sugar content have an influence on the maximum rate that IVIG can be infused. The acute renal failure that may develop is usually an acute tubular necrosis that is reversible when stopping the IVIG or when decreasing the rate of administration. It tends to occur in people with pre-existing renal disease and who are volume depleted. It seems to be more common in the elderly and diabetic patients, who tend to become dehydrated. Consequently, before beginning IVIG infusion ensure that the patient is adequately hydrated, make sure the product is sufficiently dilute and do not exceed the manufacturer's rate of administration.

The high cost of therapy and the concern about tolerability of infusion rates raises the question as to whether or not a test dose of 1 g of IVIG given over 1 hour would predict a patient's response to normal doses of IVIG. Unfortunately, there are no reports using test doses of immunoglobulins to determine response. There was a recent case report of an anaphylactoid reaction to IVIG.¹⁴ In this case report they indicated that there have only been 5 reported cases of anaphylactic or anaphylactoid reactions to IVIG. Since anaphylactic or anaphylactoid reactions are so uncommon, an IVIG test dose is rarely used to determine how patients respond to treatment.

Thrombotic events have been associated with the administration of intravenous immune globulin. Rapid infusion of IVIG has been identified as a possible risk factor. Infusion concentration should be no more than 5% and infusion rates should be no faster than 0.5 mL/kg/hr, increased slowly to a maximum rate of 4 mL/kg/hr if well tolerated in patients with thrombotic risk factors such as coronary artery disease, hypertension, cerebrovascular disease and diabetes mellitus¹⁵. For some indications this target infusion rate can be as high as 360 mL/hr. High infusion rates are not always tolerated.

The question arises as to whether or not there is any therapeutic benefit using a slow continuous infusion, rather than pulsing large doses once or twice a week. Chandramouli¹⁶ described 2 case reports where 2 patients with immune thrombocytopenia purpura (ITP) were treated with 1 g/kg continuous IVIG infusion over 24 hours with concomitant platelet infusion. In the first case, IVIG 0.4 mg/kg was infused over 10 hours followed by

platelet transfusion resulting in a platelet count of 63,000. Her platelet count subsequently dropped to 27,000 the next day. She then received a second 1 g/kg IVIG infusion, however this time it was given over 24 hours and her platelet count was maintained at 100,000/ μ l for 4 days. On day 5 she received another course of 1 g/kg 24-hour infusion IVIG and her platelets were maintained at >100,000/ μ l for 1 month except for 2 days. The patient in the second case had her platelet count rise to >96,000 after administration of 1 g/kg continuous IVIG infusion over 24 hours with concomitant platelet infusion. In both patients the treatment was well tolerated.

In a study by Kress¹⁷, anergic patients undergoing cardiac surgery were treated with polyvalent intravenous human immunoglobulin to prevent post-operative infection. Treatment began with 100 mL of IVIG infused at a rate of 33 mL/hr for 3 hours. This was followed by a constant infusion of 6 mL/hr over 50 hours with a total dose of 20 g administered in 400 mL. This treatment regimen decreased the incidence of post-operative infection (vs. placebo) but did not alter the length of hospital stay.

In the context of the above mentioned reports, IVIG has been administered as a continuous IV infusion with continued efficacy and no adverse effects. One of the case reports demonstrated a better response with the 24-hour infusion compared to 10-hour infusion. It is worth noting that none of these situations involved infusion durations greater than 50 hours. No controlled studies are available that compared the safety and efficacy of pulsed and continuous infusions for most indications; however, there is some anecdotal evidence that continuous infusion may be acceptable for certain indications.

Special Administration

Considerations – Renal Failure

There are times when IVIG must be used in patients with renal failure on hemodialysis. Immunoglobulins are high molecular weight compounds that would not be expected to be removed by dialysis. Consequently, there has not been much interest in investigating whether or not IVIG is removed by hemodialysis. However, Kagan and coworkers¹⁸ made an observation that there is a decrease in the body's natural immunoglobulins in patients receiving chronic ambulatory peritoneal dialysis. Bouts¹⁹ and coworkers made a similar observation, however, they indicate that it is not possible to know if the decrease is

due to removal by peritoneal dialysis, or decreased production of the immunoglobulins during chronic renal failure.

Dixit²⁰ and colleagues, in contrast, report that there is an increase in the circulating immunoglobulins in young hemodialysis patients. They confirmed that in their study population, using other measures of dialysis, that all patients had received adequate dialysis. Therefore, it appears that normal dialysis is not able to reduce elevated normal circulating immunoglobulins.

Dilhuydy²¹ and coworkers and Ruggeri²² and colleagues presented several cases of acute renal failure that developed after high doses of IVIG. The renal failure resolved after hemodialysis. It is unclear whether the renal failure resolved because high levels of immunoglobulin were reduced by hemodialysis or because there was another cause of the acute renal failure that resolved by the dialysis. Dilhuydy suggests that it may be the sucrose content of the IVIG preparation that produced the renal failure. Therefore, a reduction in sugar content by the dialysis resulted in a resolution of the acute renal failure, not removal of immunoglobulins resulting in resolution of the renal failure.

Based on limited information, immunoglobulin molecules are not dialyzed by traditional dialysis methods. There should be no need to adjust the dose or supplement the dose of IVIG during dialysis.

Special Administration Considerations – Obesity

Kasperck and Wetmore²³ in a letter to the editor speculated in 1990 that if IVIG could be dosed on something other than actual body weight in obese patients there would be a significant cost savings and likely avoid some adverse effects. They intuitively believed that it made sense to not dose on actual body weight in an obese individual; however, they carefully searched the literature and could not find any information to support the dosing of IVIG with either lean body mass or a corrected body weight. They contacted four manufacturers and none would or could provide them with information that IVIG could be dosed using an adjusted body weight. Even though they projected a 36% cost savings by dosing on ideal body weight they could not find sufficient evidence to support this approach. Three years later Woolfrey and Dewar²⁴ presented a case report where they did administer IVIG based on lean body mass to a single patient. They were able to show an increase in platelet count, but it was short-lived. Because it was only a single case it does not provide enough evidence to establish an

association between the short lived response and the reduced dose. There is no justification for dosing IVIG on something other than actual body weight, although intuitively it would make sense. This is an area that definitely needs further clinical investigation.

Special Administration Considerations – Premedication

There is some clinical evidence that suggests a possible association between the administration of IVIG and thrombotic events.²⁵⁻²⁷ Go and Call²⁸ reviewed the literature and discussed two possible mechanisms for this complication. The first is an increase in the viscosity of blood following administration of the IVIG. This is possibly related to the concentration of the IVIG and the rate at which it is administered. There is no pretreatment that can alter this. It is important to make sure that the patient is adequately hydrated before infusing IVIG and then, if possible, do not use high concentrations of IVIG and do not administer the dose too rapidly. The other potential cause is an IVIG activation of platelets. It would make sense that aspirin, which interferes with platelet aggregation, could play an important role here, but neither this paper, or any other, advocate the routine use of aspirin, or any other agent, to block platelet aggregation as premedication.

Another potential complication of IVIG administration is the development of headaches. Most of the drug compendia do not address the premedication regimens given for IVIG except the *American Hospital Formulary Service (AHFS)*.¹¹ AHFS suggests that oral antihistamines and analgesics may alleviate these headaches and have been used for pretreatment in those patients who had post-transfusion headaches following induction therapy for idiopathic thrombocytopenia purpura and required additional IVIG therapy. In a review of the use of IVIG in immune-mediated neuropathies, Brannagan²⁹ described in detail the complications of IVIG therapy. He indicated that persistent reactions can be controlled by treatment with 50 to 100 mg IV hydrocortisone. He also indicated that headaches usually respond to treatment with acetaminophen and migraines will respond to propranolol or other migraine treatments. He went on to say that pre-treatment with corticosteroids is not helpful. This would suggest that pretreatment with these agents is only recommended when the patient has developed one or more of these complications with previous therapy.

Stiehm²⁹ recommended a routine pre-treatment protocol of aspirin 15 mg/kg/dose or acetaminophen 15 mg/kg/dose,

diphenhydramine 1 mg/kg/dose and/or hydrocortisone 6 mg/kg/dose (maximum of 100 mg) 1 hour before infusion. He went on to say that for prolonged infusions the premedication analgesic and antihistamine can be repeated after 2 hours of infusion in patients with a history of side effects from the IVIG. Those are typical pediatric doses, adult doses are 650 mg of aspirin or 650 mg acetaminophen, 50 mg of diphenhydramine and/or 100 mg IV hydrocortisone.

Conclusion

The important role of IVIG to treat an expanding array of illnesses requires that this costly medication be used as safely and efficiently as possible. The detailed procedures for the preparation of IVIG products are different depending on the techniques that the manufacturer used to prepare the product, therefore it is important to adhere to the manufacturer's recommendations for reconstituting and preparing the final IVIG product. Generally, IVIG must be administered in a separate line and not infused concurrently with other medications. Infusions pumps may be of benefit in accurately delivering IVIG that, if administered too rapidly, can have complications. Before administration begins it is important to ensure that the patient is adequately hydrated and has reasonable renal function. Patients who have developed reactions from previous administrations can be pre-treated with an analgesic, an antihistamine and/or a corticosteroid. The patient should be monitored during infusion to ensure that no thrombotic events or acute renal failure develops.

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Accreditation Information

The University of Iowa College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. The ACPE program number is 020-000-04-007-H01. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

To earn continuing education credit, complete the assessment exercise, CE registration form and program evaluation on page 5, 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 April 1, 2005 to receive credit.

CE REGISTRATION

TITLE OF EDUCATIONAL ACTIVITY (ARTICLE)
ACPE # 020-000-04-007-H01

Safe Administration of Intravenous Immune Globulin (IVIG)

NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

SOCIAL SECURITY NUMBER (OPTIONAL) _____

PHARMACY LICENSE NUMBER(S) _____

I HEREBY CERTIFY THAT I HAVE TAKEN THIS TEST:

Signature/Date

(circle the correct answer)

1. Immunoglobulin intravenous (IVIG) preparations are composed primarily of:
 - a. Immunoglobulin A
 - b. Immunoglobulin B
 - c. Immunoglobulin G
 - d. Immunoglobulin H
2. Filters can be used in the reconstitution process of IVIG, but they must be:
 - a. 5 microns or smaller
 - b. 15 microns or smaller
 - c. 5 microns or larger
 - d. 15 microns or larger
3. Which one of the following is **false** about the administration of IVIG infusions:
 - a. Inline filters should always be used.
 - b. IVIG infusions should be administered by separate tubing.
 - c. No medications can be mixed with the IVIG.
 - d. Fluconazole can be infused through a Y-site along with the IVIG.
4. Which one of the following is **true** about IVIG associated renal failure:
 - a. The acute renal failure is generally not reversible.
 - b. Renal failure occurs most frequently in patients with severe edema.
 - c. Renal failure is likely due to the increased osmolality from the increased sugar concentration.
 - d. Pump administration of IVIG will ensure that renal failure will not develop.
5. Which one of the following statements is **false** about the rate of administration of IVIG:
 - a. Acute renal failure is more likely to occur with higher administration rates.
 - b. A 1 g test dose of IVIG has been shown to predict how a patient will respond to ordinary doses.
 - c. Anaphylactic or anaphylactoid reactions are not very common with IVIG.
 - d. Slow, continuous infusions of IVIG for up to 50 hours have been shown to be safe and effective for some indications.
6. In patients who have significant, chronic renal failure:
 - a. No adjustments in dose need to be made because the drug is not dialyzed.
 - b. The dose must be increased because of IVIG removal during dialysis.
 - c. The rate of administration must be increased to ensure adequate delivery of the IVIG.
 - d. The rate of administration must be decreased by 50% to prevent further renal damage.

7. Dosing of IVIG based on ideal body weight or a corrected body weight:
 - a. Would result in a negligible cost savings in an obese patient.
 - b. Is currently recommended by most manufacturers.
 - c. Has been shown to be just as effective as using actual body weight.
 - d. Is an area that definitely needs further investigation.
8. The increased viscosity of IVIG preparations can further increase the viscosity of blood. This can increase the chance of a patient having:
 - a. A thrombotic event.
 - b. A migraine headache.
 - c. A bradycardia (slow heart rate).
 - d. A hypertensive crisis.
9. Post-transfusion migraines can usually be relieved by:
 - a. Phenytoin.
 - b. Propranolol.
 - c. Fluconazole.
 - d. Adequate hydration.
10. If previous treatment indicates a transfusion reaction is likely, a typical pre-treatment protocol 1 hour before infusion would include all of the following **except**:
 - a. Acetaminophen 650 mg.
 - b. Diphenhydramine 50 mg.
 - c. Dicyclomine 50 mg.
 - d. Hydrocortisone 100 mg IV.

PROGRAM EVALUATION

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

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

New Drugs: Key References

This new drug bibliography provides a selection of key critical studies and reviews of new drugs approved by the FDA December 2003 through January 2004. An *IDIS* search retrieved articles relevant to the new drugs and their approved uses.

Abarelix

Tomera K, Gleason D, Gittelman M, Moseley W, et al. The gonadotropin-releasing hormone antagonist abarelix depot versus luteinizing hormone releasing hormone agonists leuprolide or goserelin: initial results of endocrinological and biochemical efficacies in patients with prostate cancer. *J Urol.*2001; 165:1585-1589. (*IDIS* Article Number 465895)

This Phase 2 open-label study, that treated 242 prostate cancer patients requiring initial hormonal treatment with either abarelix 100 mg intramuscular depot every 28 days plus one injection on day 15 or leuprolide depot in 1, 3 or 4-month formulations or goserelin depot in 1 or 3-month formulations, with or without antiandrogens, found that the primary endpoint of medical castration was achieved by day 8 of drug administration in 75% of the patients using abarelix and 0% of the patients treated with leuprolide or goserelin.

Trachtenberg J, Gittleman M, Steidle C, Barzell W, et al. A Phase 3, multicenter, open-label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer. *J Urol.*2002; 167: 1670-1674. (*IDIS* Article Number 478367)

In this Phase 3 open label study, 255 patients with prostate cancer were randomized to 100 mg depot of abarelix or 7.5 mg intramuscular injection of leuprolide every 28 days for 24 weeks. Researchers found abarelix more effective (p<0.001) in avoiding testosterone surge and more effective (p<0.001) at reduction of testosterone to medical castration levels in the first 8 days than leuprolide plus antiandrogen.

Tadalafil

Brock GB, McMahon CG, Chen KK, Costigan T, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol.*2002; 168: 1332-1336. (*IDIS* Article Number 487266)

This integrated analysis of five multicenter, randomized, double-blind, placebo-controlled trials of 1,112 men age 18 years or older with erectile dysfunction, treated with tadalafil fixed oral daily doses of 2.5, 5, 10 or 20 mg, measured effectiveness based on the International Index of Erectile Function (IIEF), Sexual Encounter Profile (SEP) and Global Assessment Question (GAQ) and found that tadalafil was well tolerated and significantly improved all efficacy outcomes (p<0.001) compared with placebo.

Saenz de Tejada I, Anglin G, Knight JR and Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care.*2002; 25:2159-2164. (*IDIS* Article Number 496492)

Researchers conducted a multicenter, placebo-controlled, double-blind, parallel-group study of 216 men 18 years of age or older with diabetes and erectile dysfunction who were randomly allocated to tadalafil oral doses of 10 mg or 20 mg up to once a day for 12 weeks or placebo, and using the International Index of Erectile Function (IIEF), researchers found that tadalafil significantly improved all aspects of primary efficacy (p<0.001) and was well tolerated by men with diabetes without significantly changing HbA1c levels.

Tiotropium Bromide

Casaburi R, Briggs DD, Donahue JF, Serby CW, et al. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD. *Chest.* 2000; 118:1294-1302. (*IDIS* Article Number 455668)

Researchers studied the safety and bronchodilator efficacy of tiotropium in this randomized, double-blind, placebo-controlled, multicenter trial of 470 patients with COPD who were randomized to receive once daily inhalation dosing of 18 mcg of tiotropium or placebo, and found that tiotropium was significantly more effective than placebo in both trough and average FEV₁ and FVC response (p <0.001) with a low incidence of side effects.



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

Littner MR, Ilowite JS, Tashkin DP, Friedman M, et al. Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2000; 161:1136-1142. (IDIS Article Number 446065)

This was a randomized, double-blind, placebo-controlled, multicenter, parallel group study to evaluate the dose response of tiotropium once daily doses of 4.5, 9, 18, or 36 mcg inhalation powder administered to 162 COPD patients for 4 weeks. Researchers found significant improvement in FEV₁ and FVC within 1 hour after 4.5 to 36 mcg doses of tiotropium (p <0.05) and a safety profile similar to placebo.

Donahue JF, van Noord JA, Bateman ED, Langley SJ, et al. A 6-month placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; 122:47-55. (IDIS Article Number 484065)

A total of 623 COPD patients at 39 centers in 12 countries participated in this randomized trial to test the safety and efficacy of tiotropium 18 mcg once a day inhalation powder or salmeterol 50 mcg twice a day inhalation aerosol compared to placebo, and researchers found that tiotropium once daily was more effective for bronchodilation, improvement of dyspnea and in achieving meaningful improvement in health related quality of life.

FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) Trade Name	Sponsor (Approval Date)	IDIS Drug Term Drug Number (IDIS Citations)*	Indication/Use	IDIS Disease Term Modified ICD-9-CM Number
Abarelix (1P)***** <i>Plenaxis</i>	Praecis (Nov. 25, 2003)	ABARELIX 68180904 (8 citations)	Prostate cancer.	Neop, Mgn-Prostate 185.
Sertaconazole Nitrate (1S)** <i>Ertaczo</i>	Mylan Pharms (Dec. 10, 2003)	SERTACONAZOLE 8120517 (7 citations)	Tinea pedis.	Dermatophytosis, Foot 110.4
Tiotropium Bromide (1S) <i>Spiriva Handihaler</i>	Boehringer Ingelheim (Jan. 30, 2004)	TIOTROPIUM BROMIDE 12080059 (29 citations)	Chronic Obstructive Pulmonary Disease COPD (including chronic bronchitis and emphysema).	Obstruction, Air, Chr NEC 496. Emphysema NEC 492. Bronchitis, Obstructive, Chr 491.2
Tadalafil (1S) <i>Cialis</i>	Lilly Icos (Nov. 21, 2003)	TADALAFIL 24120103 (26 citations)	Erectile dysfunction.	Impotence, Organic 607.84

* Through January 2004 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.

+ Accelerated Approval.

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 selectively indexed and included as part of the IDIS database as they become available. Use descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the database.

Safety of Paxil® in children and adolescents—what can you tell clinicians and patients?

Perspective from an



IDIS Subscriber

Background

The development of selective serotonin reuptake inhibitors (SSRIs) in the 1980's for the treatment of major depressive disorder (MDD) added a new option to the pharmacotherapy of depression. The absence of sedative and anticholinergic adverse effects, coupled with relative safety in overdose, and presumed equal efficacy resulted in widespread interest in their use. Within a few years of their availability, some authors suggested the older tricyclic antidepressants (TCA) should no longer be considered first-line treatment for depressive disorders. In 1993 the American Psychiatric Association's¹ practice guideline for MDD in adults included TCAs, SSRIs, and monoamine oxidase inhibitors as equally effective antidepressants for the treatment of uncomplicated first-episode major depression.

However not all authors were ready to abandon TCAs. Potter² and colleagues, at the Clinical Pharmacology and Experimental Therapeutics group at the National Institute of Mental Health, considered SSRIs to be second line agents for patients with more severe depression. They noted that reports suggesting the possibility of fluoxetine-induced suicidal ideation had generated well-publicized concern, but had not been supported by larger clinical studies. Owens³, in the less optimistic of a pair of editorials in *BMJ* on the benefits of newer antidepressants including SSRIs, suggested the benefits of the newer drugs were exaggerated. He described a different adverse effect profile

for SSRIs including common complaints of nausea and diarrhea and less frequent reports suggesting that the central nervous system might be affected including insomnia, agitation, extra-pyramidal symptoms and withdrawal effects. In his opinion when the drop out rates from 58 antidepressant trials were properly reviewed, about a third of patients dropped out of each drug group. He concluded that the older compounds whose effectiveness and long term ill effects were known from many years of widespread use should remain first line treatment for depression. Only when the change to SSRIs seems certain to be of benefit, should they replace the older antidepressants. A later editorial by Schatzberg⁴, from the Department of Psychiatry at Stanford University, stated, "many academics ... question whether it (Prozac®) is as effective as the older TCAs or monoamine oxidase inhibitors in a number of special circumstances-e.g., severe depression, atypical depression." A decade after their introduction, he believed additional data on both the relative efficacy and tolerability of SSRIs is needed. Further study is needed before the proper place of SSRIs in the treatment of depression can be finally determined.

However, the pattern of use of antidepressant drugs in the United States was changed dramatically by the availability of SSRIs. By the year 2002 Zoloft® was ninth, Paxil® was tenth, Celexa® was twentieth, and Effexor XR was twenty-first on the list of "Top 200 Drugs of 2002" in total sales

dollars in the United States. Generic fluoxetine HCl was 120th on the list and no TCA was among the top 200 drugs.⁶

Depression and suicidal ideation and behavior

A major confounding factor in the evaluation of possible drug associated suicide is the occurrence of suicidal ideation, suicide attempts, and completed suicide in untreated depressed patients. Depressed patients can seek treatment at any point in their illness, they may become suicidal before pharmacotherapy is begun or during treatment.

Age is one of the demographic factors, that influences suicide rates. Between the ages of 10 and 24 years, suicide rates in the general population of the United States increase to approximately 13 per 100,000. Suicide rates in most age groups have remained stable over the past half-century; the rate among adolescents and young adults has increased. In the 14 to 25 year-old age group, the suicide rate is triple the rate in the 1950s.⁵

The American Psychiatric Association⁵ has issued guidelines for the evaluation and assessment of patients with suicidal behavior. The guideline contains an extensive list of factors that have been associated with an increased risk of suicide. The estimation of suicide risk is one of the classic problems in clinical

judgment; no known specific risk factor or set of risk factors can predict suicide or suicidal behavior. McAlpine⁷ has focused on the higher risk of suicide in patients with affective disorders and alcoholism and offered a list of warning signs.

Case Reports

Interest in SSRIs and suicide risk increased after the suggestion that Prozac® might be responsible for the emergence of "intense suicidal preoccupation" in an uncontrolled group of adults being treated for depression. This small group of depressed patients, free of recent serious suicidal ideation, developed a new syndrome within 2-7 weeks of starting fluoxetine. The group was described as hopeful and optimistic before fluoxetine was begun and without preexisting self-destructive urges. The obsessive suicidal thoughts only began after weeks or months of fluoxetine treatment. Two of the six patients who developed suicidal ideation were taking only fluoxetine. Four of the six patients complained of a sense of "inner restlessness," they may have been describing a form of akathisia. Teicher⁸ and colleagues observed this type of side effect in 3.5% of their patients on fluoxetine. Their group had started to inform patients of this risk and instructed them to call if they developed side effects or they felt worse.

A few months later, King⁹ and colleagues published a compelling case series of six young patients, receiving fluoxetine for obsessive-compulsive disorder, who developed “intense self-injurious ideation and/or behavior.” Before beginning fluoxetine four of the six patients were described as having major risk factors for self-destructive behavior. De novo or worsened self-injurious ideation or behavior emerged, requiring psychiatric hospitalization in four of the six cases. The time interval between beginning fluoxetine therapy and the appearance of the new syndrome ranged from 1 to 6 months. In one case the syndrome appeared shortly after the fluoxetine dose had been increased to 60 mg/day in a patient who had tolerated lower doses for approximately a year without any similar symptoms. In two other cases second trials of fluoxetine resulted in the return of suicidal ideation about two months later.

In 1992, Wirshing¹⁰ and colleagues published another uncontrolled case series, of five depressed female patients without a significant history of suicidal behavior, who became suicidal during treatment with fluoxetine. The experience in their group did not involve worsening depression, but instead a “novel somatic-emotional state” which they thought might be fluoxetine-induced akathisia. All patients experienced “an urge to pace” which corresponded with the intensity of their distress. All experienced suicidal thoughts at the peak of the syndrome. Importantly, all

reported resolution of their agitation, restlessness, pacing urge, and suicidal thoughts after fluoxetine was discontinued.

Cases of possible antidepressant-related akathisia were described prior to the introduction of SSRIs¹¹. Interested readers will find several reviews of the clinical details of the various akathisia syndromes.^{12,13,14} Mann and Kapur¹⁵ reviewed the early 1990’s case reports of suicidal ideation or behavior temporally associated with antidepressant therapy.

Clinical Trials

Before reviewing the results of clinical trials on the subject of SSRIs and suicide, the advice of Wirshing¹⁰ and colleagues is important.

“Examining large, placebo-controlled databases for treatment emergent suicidal ideation is not likely to be instructive because the active treatment, even if it causes suicidal ideation in a sub-group, also suppresses it. As long as the treatment (fluoxetine) suppresses more suicidal ideation than it induces, it will compare favorably with the placebo group.”

Kahn¹⁶ and colleagues recently analyzed reports from randomized controlled trials to compare suicide rates in patients treated with SSRIs, other antidepressants, or placebo. FDA data was obtained for the period from January 1985 to January 2000 for nine antidepressants eventually approved for use in the United States. Of 26,109 patients randomized to an SSRI there were 38 suicides, a rate of 0.15%. Among the 17,273 assigned to other antidepressants there were 34 suicides, a rate of 0.20%. Of the 4,895 assigned

to placebo there were 5 suicides, a rate of 0.10%. Their finding did not support a difference in suicide rates between, SSRIs, other antidepressants, and placebo. They reported that the possibility of SSRIs increasing suicide rates remains to be proven or disproven. They reminded us that antidepressant clinical trial participants are not equivalent to the range of clinically depressed patients. Most patients with any history of attempted suicide or active suicidal thoughts are excluded from antidepressant trials, as are patients with psychotic features or refractory depression. Their results suggest that the class of antidepressant used has minimal effect on suicide rates in clinical trials.

Kahn¹⁷ and colleagues also analyzed reports from randomized controlled trials of antidepressants to compare suicide rates in patients treated with placebo with the active treatment. They found that patients assigned to placebo were not at higher risk of suicide or suicide attempts than those assigned to active treatment.

Beasley¹⁸ and colleagues at Lilly Research Laboratories, conducted several meta-analysis on fluoxetine and suicide in various psychiatric disorders. A retrospective examination of the pooled data from seventeen double-blind clinical trials in patients with MDD comparing fluoxetine (n=1765), with a TCA (n=731) or placebo (n=569) or both was conducted. The incidence of emergence of significant suicidal ideation was 1.2% for fluoxetine, 2.6% for placebo, and 3.6% for TCA. The pooled incidence of worsening of suicidal

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. WE WELCOME COMMENTS. IF YOU ARE INTERESTED IN SHARING YOUR EXPERIENCES USING THE IDIS DATABASE, PLEASE CONTACT DONNA-BRUS@UIOWA.EDU

ideation was 17.9% for placebo, 16.3% for TCA and 15.3% for fluoxetine. Improvement in suicidal ideation was 72.2% for fluoxetine, 69.8% for TCA and 54.8% for placebo. They concluded data from the clinical trials did not support the belief that fluoxetine is associated with an increased risk of suicide or emergence of suicidal thoughts in the clinical trial patients. In another retrospective review of pooled data from clinical trials in which fluoxetine (n=266) was compared to placebo (n=89) in the treatment of obsessive-compulsive disorder there was no evidence of increased suicidality in patients treated with fluoxetine.¹⁹

More recently Walsh and Dinan²⁰ have reviewed the literature on SSRIs and violence. They did not find any convincing evidence to link SSRIs to violence or suicide. They consider the recent lay media reports potentially dangerous, increasing the concerns of depressed patients who are prescribed antidepressants.

Drug Regulators - UK

On June 10, 2003 the Chairman of Committee on Safety of Medicines sent a

“Dear Colleague” letter to clinicians in the UK advising them of new evidence on the efficacy and safety of paroxetine in children and adolescents under the age of 18 when used to treat depressive illness. Data from clinical trials received in May 2003 “did not demonstrate efficacy in depressive illness in this age group and indicated an increase in the risk of harmful outcomes including episodes of self-harm and potentially suicidal behavior in the paroxetine treated group compared to placebo.” Paroxetine should not be used in children and adolescents under the age of 18 for treatment of depression.²¹

Three months later on September 19, 2003 another “Dear Colleague” letter focused on new evidence which did not demonstrate efficacy and indicated an increase in the rate of harmful outcomes, including hostility, suicidal ideation and self-harm in the venlafaxine group compared with the placebo group. There were 3 suicide attempts in the venlafaxine group and none in the placebo group. There were no completed suicides. A warning against the abrupt discontinuation of venlafaxine due to the risk of withdrawal reactions was also included. Venlafaxine should not be used in children and adolescents under the age of 18 for treatment of depression.²²

Most recently, on December 10, 2003 another “Dear Colleague” letter was sent, this time as an “Urgent Message”. This message indicated that the “Expert Working Group” had completed its review on the safety and efficacy of the SSRI class in the treatment of pediatric MDD. Committee on Safety of Medicines (CSM) has advised on the basis of the recently completed review of pediatric clinical trial data, that the balance of risks and benefits for treatment of MDD in patients under the age of 18 is judged to be unfavorable for sertraline, citalopram and escitalopram and

is unassessable for fluvoxamine. Only fluoxetine has clinical trial data in young people judged to have a favorable risk benefit ratio. In adults, based on evidence to date, the benefits of treatment are considered to outweigh the risks for all SSRIs.²³

Drug Regulators - USA

On June 19, 2003 the FDA issued a public statement on the use of the antidepressant Paxil® for the pediatric population. The message indicates the FDA is currently reviewing safety information from three well-controlled trials in pediatric patients with MDD. These trials failed to show any benefit of paroxetine over placebo. They reference the UK’s conclusion of increased rate of self-harm and potentially suicidal behavior in the pediatric age group when paroxetine is used to treat depression. They are careful to point out that despite potential safety concerns patients taking Paxil® should not suddenly discontinue use of the drug.²⁴

Four months later on October 27, 2003 the FDA issued a Public Health Advisory^{25a} and Dear Health Care Professional Letter^{25b} entitled: Reports of suicidality in pediatric patients being treated with antidepressant medications for major depressive disorder. They have now completed a preliminary review of data for 8 antidepressant drugs (citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine) studied under the pediatric exclusivity provision. That data is consistent with an excess of such reports in young patients treated with the antidepressant drugs compared to those assigned to placebo. A meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee was scheduled for February 2, 2004. The meeting was adjourned and

will be reconvened at a later date. Any FDA regulatory action(s) will be announced after the committee’s work is completed and a final determination is made by the agency.

The public health advisory mentions press and medical journal reports of suicide attempts and completed suicides in young patients on antidepressant therapy. Such reports are difficult to evaluate in the absence of any control group data, as these events also occur in untreated patients with depression. There were no reports of completed suicides in over 4,100 pediatric patients entered in placebo-controlled trials. At this time only fluoxetine has established efficacy in the treatment of MDD in pediatric patients. The advisory concludes with a warning about the abrupt discontinuation of these drugs and refers the reader to labeling for individual drugs.

At this time, the FDA has reemphasized its statements on the possibility of suicide attempts in MDD and warnings about abrupt discontinuation of antidepressant therapy.

Comment

Whether or not SSRIs can infrequently or rarely “cause” suicidal behavior or actual suicide attempts is unresolved. One review suggests the most convincing cases linking fluoxetine and suicidal behavior were three cases who all developed severe akathisia and attempted suicide while taking fluoxetine alone in daily doses of 40 mg or 60 mg. The suicide attempts each occurred within a week of a fluoxetine dose increase. In each case when the patient was rechallenged with fluoxetine, the akathisia and suicidal thoughts returned. In two cases the akathisia was successfully treated with propranolol, a common treatment for neuroleptic-induced akathisia.¹⁸ These reports plus a number of other reports, including a few with positive rechallenges, have provided support for the belief

that adverse reactions involving suicidal ideation and behavior may occur with fluoxetine and other SSRI use.

The occurrence of symptoms such as: anxiety, nervousness, restlessness, anxiety, agitation, as possible side effects of SSRI use have been differently named as hypomania, psychic akathisia, or behavioral activation which refer to different possible etiological mechanisms. Clinical judgment is required to decide if a patient’s syndrome is akathisia, or hypomania or behavioral activation. Different groups, the manufacturers, psychiatrists, physicians studying chemically induced syndromes, and the public have differing interests when naming such clinical syndromes. The etiologic mechanism(s) of these syndromes with a temporal relationship to SSRI use is not established. Any description or discussion of the importance of specific mechanisms for the syndrome is speculative at this time.

Antidepressant related akathisia has been reported with other classes of antidepressants, although very infrequently.¹¹ Suicide attempts have been associated with akathisia and neuroleptics.²⁶ Akathisia has also been reported in 50% of a small group of patients taking metoclopramide as an antiemetic for cancer chemotherapy. Seventy-five percent of them had not reported their syndrome to their physician. The syndrome was only discovered by the use of a structured interview with specific questions relating to akathisia.²⁷

Akathisia may be associated with a state of severe subjective distress, which some patients find unacceptable. Depressed patients who experience increasing agitation or other unpleasant side effects may believe their new syndrome is the result of a worsening of their illness not a side effect of medication. In such a situation, increased hopelessness and despair may result.

Even though it has not been established that SSRIs alone can cause increased suicidal behavior or increased suicide rates in treated patients and we do not know how frequently such syndromes occur in patients outside the clinical trial setting, this situation demands close attention.

A recent issue of the *Medical Letter on Drugs and Therapeutics*²⁸ addressed the issue of SSRIs and suicidality in children. It stated:

“There are no convincing data showing that SSRIs, including paroxetine, are any less safe in children than in adults. Medical Letter consultants believe all of these drugs are much more likely to prevent suicide than to cause it.”

Until this problem is resolved, clinicians should consider informing depressed patients beginning SSRI therapy that “depressive symptoms and/or a worsening or emergence of suicidal behavior may occasionally occur during treatment. The patient should be instructed to immediately inform the clinician should these symptoms occur. How this warning can be effectively communicated to a young child and their parents presents a special challenge.

Unless patients are informed about the possibility of such adverse effect syndromes and the need to report them, their frequency will never be known. Only if the patients who report such syndromes complete structured interviews searching for symptoms of akathisia, will the debate about activation vs. akathisia be resolved.

The recent focus on this issue by regulatory agencies and the increased awareness by clinicians should lead to increased awareness by patients. Hopefully this knowledge will translate into less suicidal behavior possibly related to antidepressant use.

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