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## Drug Treatment of the Complications of Refractive Surgery: LASIK, LASEK and PRK

### Learning Objectives

1. Describe the procedure for laser in-situ keratomileusis (LASIK), photorefractive keratectomy (PRK), and laser subepithelial keratomileusis (LASEK) and the differences between the three procedures.
2. Discuss post-operative diffuse lamellar keratitis (DLK) and infectious keratitis and their treatment.
3. Explain issues of concern for post-operative corticosteroid use.
4. Describe characteristics of infectious keratitis.

### About the Author:



Brad Gilchrist is a 1990 graduate of the University of Iowa College of Pharmacy (B.S., R.Ph.). His current position at DDIS is Staff Pharmacist II-Academic Research. In addition to indexing articles for the database, his other main responsibility is overseeing the acquisition, formatting and indexing of the FDA Approval Packages.

### Introduction

In the year 2000, nearly 1.3 million laser in-situ keratomileusis (LASIK) procedures were performed in the United States.<sup>1</sup> In a 2003 survey of U.S. ophthalmology surgeons, LASIK was the most commonly performed refractive surgery.<sup>2</sup> Photorefractive keratectomy (PRK) and laser subepithelial keratomileusis (LASEK) were noted as alternatives to LASIK with bright futures. Each procedure has its pros and cons and no one procedure is best suited for all patients. The trend in surgical correction of refractive errors is likely to continue as the current procedures evolve and technology advances.

### The Eye

The basic components of the human eye include the cornea, pupil, lens, retina and optic nerve.<sup>3</sup> The cornea and lens work in conjunction to focus and bend, or refract, light entering the eye to form a single focal point of an image on the retina that is then transmitted via the optic nerve to the brain. The overall shape of the eye and imperfections in the cornea or lens can result in refractive error and instead of the focal point focusing directly on the retina, the image focal point lands in front, behind or on multiple points of the retina resulting in a perceived blurry image (**Figure 1**).<sup>4,5</sup>

### Refractive Errors

Three types of refractive errors are myopia, hyperopia and astigmatism.<sup>4</sup> In emmetropia, or a normal eye, the focal point of the refracted light lands directly on the retina (**Figure 1**).<sup>5</sup> Myopia, or nearsightedness, occurs when the focal point of an image lands in front of the retina due to the eye being too long or the cornea curvature too steep (**Figure 1**).<sup>5</sup> Persons who are myopic or nearsighted can clearly see objects close by but objects at a distance are blurry or out of focus. Hyperopia, or farsightedness, is a condition in which the focal point of an image lands behind the retina due to the eye being too short and the cornea too flat (**Figure 1**).<sup>5</sup> Persons who are farsighted can clearly see objects at a distance but objects nearby are blurry or out of focus. In astigmatism, no single focal point is formed. Light falls on many points of the retina causing distorted vision (**Figure 1**).<sup>5</sup> Corrective lenses in the form of eyeglasses or contact lenses are used by many to correct for nearsightedness, farsightedness and astigmatism. Refractive surgery to correct refractive errors is an alternative for many persons in need of corrective lenses.

## Refractive Surgeries

LASIK, PRK and LASEK are 3 of the more commonly performed refractive surgeries.<sup>2</sup> During LASIK surgery, a highly sophisticated “knife,” called a microkeratome, is used to make an 80-200 micrometer thin corneal flap.<sup>6</sup> The middle section, or stroma, of the cornea is revealed when this hinged corneal flap is folded back. Next, computer-controlled excimer laser pulses vaporize predetermined portions of the corneal stroma, permanently reshaping the cornea. When the procedure is finished, the flap is repositioned over the cornea and adheres without sutures.<sup>5</sup> Post-operative pain is minimal, functional visual recovery typically occurs in less than 24 hours and visual stability is achieved from 1-6 weeks.<sup>6</sup>

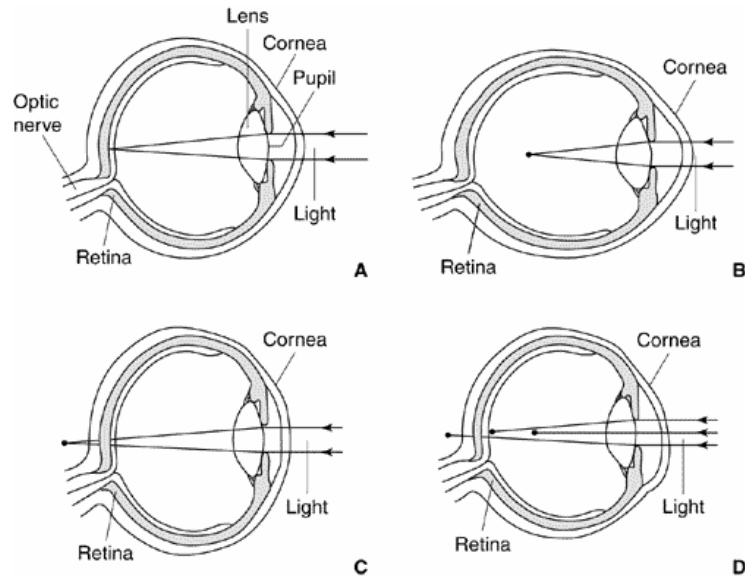
In PRK and LASEK, a laser is also used to reshape the cornea. The main procedural difference between LASIK, PRK and LASEK is the way in which the stromal layer of the cornea is exposed. During LASEK, 18-20% ethanol is used to breakdown the epithelial layer of the cornea. The epithelial layer is left somewhat intact but is moved aside to perform the laser recontouring.<sup>6</sup> After the stromal layer of the cornea has been reshaped, the epithelial layer is moved back over the cornea and a bandage contact lens is inserted to protect the eye.<sup>5</sup> In 3 or 4 days, after the epithelial layer has regenerated, the contact lens is removed. During PRK, the epithelial layer of the cornea is physically scraped away revealing the stromal layer of the cornea that is then reshaped with the laser.<sup>5</sup> In both PRK and LASEK, post-operative pain is mild to moderate, lasting 24-48 hours and functional vision typically returns in 3 to 7 days while vision stabilization may take from 3 weeks to several months.<sup>6</sup> LASEK and PRK are recommended over LASIK in persons with thin corneas and in people who are very active or involved in sports due to the possibility of flap dislodgement.<sup>6</sup> No particular refractive surgery is ideal for all patients. Each procedure has its own advantages and disadvantages. The ultimate decision is up to the patient and their surgeon.

## Post-Operative Infection

Although relatively infrequent, post-operative infection is a concern of refractive surgery. Pre-operative antibiotics have been shown to significantly reduce the bacterial flora of the eye. Three days before PRK surgery, conjunctival swabs were taken from 100 eyes of 70 healthy patients.<sup>7</sup> From these 100 eyes, 191 independent bacterial isolates were cultured. Of these isolates, *Staphylococcus epidermidis* and *Staphylococcus aureus* were the most frequently occurring. After 3 days of ofloxacin 0.3% eye drops 3 times daily,

nearly all the normal ocular gram-positive, gram negative and anaerobic bacterial species had been eliminated. Bacteria could be isolated from only 7 of the 100 eyes.<sup>7</sup> Broad spectrum antibiotics such as the fluoroquinolones are routinely used after refractive surgery. In a survey completed by 135 U.S. members of the International Society of Refractive Surgery of the American Academy of Ophthalmology, moxifloxacin, gatifloxacin, ofloxacin, levofloxacin, ciprofloxacin, tobramycin and gentamicin were the most commonly prescribed postoperative antibiotics in the years 2002 and 2003.<sup>2</sup>

In 2 separate studies, a significant increase was seen in the resistance of *Staphylococcus aureus* to ciprofloxacin, levofloxacin and ofloxacin.<sup>8,9</sup> From 1993 to 1997, resistance of *S. aureus* to ciprofloxacin increased from 5.8% to 35.0% and for ofloxacin from 4.7% to 35.0% in bacterial keratitis clinical isolates.<sup>8</sup> Similarly, in another study, resistance to ciprofloxacin in *S. aureus* isolates from keratitis and conjunctivitis increased from 8% during 1990-1995 to 20.7% during 1996-2001.<sup>9</sup> In this same study, from January 2000 to December 2001, the *S. aureus* resistance rate for levofloxacin was 25.5%.



**Figure 1 Errors of refraction.** (A) Emmetropia; (B) myopia; (C) hyperopia; (D) astigmatism.

From *The Merck Manual of Diagnosis and Therapy*, Edition 17, p. 743, (<http://www.merck.com/mrkshared/mmanual/figures/102fig1.jsp>) edited by Mark H. Beers and Robert Berkow. Copyright 1999 by Merck & Co., Inc., Whitehouse Station, NJ.

## Infectious Keratitis

While reportedly infrequent, infectious keratitis following PRK, LASEK or LASIK is a concern and can be a significant post-operative problem.<sup>6,10-13</sup> In 2003, a systematic review of published case reports and/or case series identified 87 patients who developed infection in 103 eyes following LASIK surgery.<sup>1</sup> The rate of infection following LASIK ranged from 0.02% (1/6312 cases) to 1.20% (1/83 cases). Of the eyes for which the information was available, 28 eyes presented with infection 2.7 days +/- 4.2 days (range: 0-7 days) following LASIK surgery. Forty-four eyes developed infection greater than 7 days after the procedure, with an average of 27.4 +/- 3.6 days (range: 10-90 days). Symptoms on presentation included pain, decreased or blurry vision, photophobia, irritation, redness, and discharge. A small percentage, however, were asymptomatic. Clinically non-significant reductions in final visual acuity occurred in 50.5% of the eyes, 24.7% had moderate reductions and 24.7% had severe reductions in visual acuity. Gram-positive bacteria and *Mycobacterium* were the most common infections followed by fungal, yeast, polymicrobial, *Acanthamoeba*, *Pseudomonas* infections and sterile cultures. The most commonly identified infections were *S. aureus* and *Mycobacterium chelonae*. Infections occurring less than 7 days after refractive

surgery are likely due to gram-positive organisms<sup>1</sup> whereas mycobacterial<sup>13,14</sup> infections typically occur more than 10 days after surgery. More severe visual problems were associated with fungal infections.<sup>1</sup>

Antibiotic therapy for bacterial keratitis is essential and often curative but does not necessarily ensure good vision. The more quickly infectious keratitis is diagnosed, causative organism identified and appropriate therapy started, the better chance for a positive outcome.<sup>15</sup> When infectious keratitis is suspected following LASIK surgery, early lifting and repositioning of the flap soon after symptom onset for culture, scraping and irrigation of the stromal bed allow for better antibiotic selection, penetration and treatment outcome.<sup>1,15</sup> There is indecision as to whether or not the addition of corticosteroids is beneficial, and if they are beneficial, when they should be initiated.<sup>1,16</sup> If the infectious agent is unidentified and effective antibacterial therapy cannot be provided, corticosteroids should be avoided.<sup>1,16</sup> Steroid eye drops increase the risk of infectious complications affecting the cornea and may worsen the situation.<sup>14,16</sup> The addition of topical corticosteroids to aid in reepithelization or minimize stromal alteration may be considered after the microorganism is identified and after 1 or more days of antibiotic therapy with noticeable improvement or no signs of worsening.<sup>1,16</sup>

## Post-Operative Corticosteroids

The use of steroids to treat inflammation not due to infectious keratitis after LASIK surgery has also been questioned. In contrast to PRK and LASEK in which comparatively large areas of the epithelial layer of the cornea is disrupted, LASIK leaves only a small ring of epithelial disruption that typically heals within a few hours. In a randomized study of 897 patients who received either artificial tears or 1 drop of 1% prednisolone acetate 4 times a day for 4 days after LASIK, no significant improvement of the accuracy of the refractive effect was noted in the prednisolone group.<sup>17</sup> A decrease in stability of the refractive outcome was noted in the more highly myopic eyes receiving prednisolone acetate. There was also no significant difference between the prednisolone and placebo group for adverse events, complications or loss of best corrected vision.

Corticosteroids are prescribed following PRK and LASEK to prevent haze, scarring and refraction regression. Haze formation or loss of corneal transparency and scarring are complications more specific to PRK and LASEK.<sup>6</sup> Haze may result from the cornea healing process.<sup>18,19</sup> Controversy exists as to whether or not post-operative corticosteroid eye drops are beneficial in preventing or treating haze. Two randomized studies showed that administering dexamethasone 0.1% drops for 3 months or fluorometholone 0.1% for 6 months had no effect on corneal haze.<sup>20,21</sup> After up to 3 months of dexamethasone 0.1%, 1 retrospective study of 100 patients concluded that haze was reduced.<sup>22</sup> A review of the use of corticosteroids after PRK determined that, from the published literature, there was no justification for the routine use of corticosteroids after PRK for low or moderate myopia but that corticosteroids may have a role in select patients.<sup>23</sup>

## Diffuse Lamellar Keratitis

Corticosteroids have been shown to be beneficial in treating diffuse lamellar keratitis (DLK). DLK is a noninfectious inflammatory reaction of the lamellar interface that typically arises within the first week of LASIK surgery, but it also can occur weeks to months later.<sup>24-26</sup> DLK has been reported to occur in 0.2-3% of LASIK patients.<sup>27,28</sup> DLK is characterized by a diffuse, white, granular, culture-negative lamellar keratitis.<sup>25</sup> This condition is also referred to as "Sands of Sahara" alluding to its white granular appearance with waves of increased density. In some eyes, the inflammation disappears almost spontaneously whereas in others, it can progress to scarring and poor visual outcomes.<sup>25</sup> In a retrospective study of 1000 LASIK eyes, 40 (4%) developed DLK.<sup>29</sup> Postoperatively all patients had received eye drops of prednisolone acetate 1% (Pred® Forte 1%) 4 times a day, ofloxacin (Ocuflox®) 4 times a day and diclofenac sodium 0.1% (Voltaren®) 4 times a day as needed for discomfort and frequent non-preserved artificial tears.<sup>29</sup> At the time DLK was diagnosed, patients were instructed to increase the frequency of the prednisolone acetate to every 1 to 2 hours. If DLK progressed to stage 3, oral prednisone was started at doses ranging from 40 to 80 mg per day. Patients received oral prednisone for 1 to 2 weeks followed by rapid taper based on clinical response. No patients in this study developed permanent loss of

corneal clarity and no eye was treated with interface irrigation or relifting of the flap. In another study of 105 eyes with DLK in 58 patients, the rate of DLK was also seen to decrease from 5.3% to 0.7% when hourly prednisolone acetate 1% or dexamethasone sodium phosphate and fluoroquinolones were initiated.<sup>24</sup> While steroids in conjunction with antibiotics are effective in treating or preventing DLK, they are not without complications. Steroid-induced glaucoma has been documented in patients receiving topical steroid drops after LASIK surgery.<sup>30,31</sup>

## Conclusion

While LASIK, LASEK and PRK are currently popular refractive surgeries, long term data on safety and effectiveness are not yet available. Post-operative haze, scarring, infectious keratitis and diffuse lamellar keratitis, while relatively infrequent, are just a few of the complications that may arise. Drug therapy for some of these complications is available but does not guarantee complete recovery. A person considering undergoing any of these procedures would be wise to research the literature and carefully weigh the risks and benefits before making their decision to have refractive surgery.

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Accreditation  
Information



The University of Iowa College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. The ACPE program number is 020-000-05-085-H01. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

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**CE REGISTRATION**

ACPE#020-000-05-085-H01

VOLUME: 16 ISSUE: 2 JUNE 2005

**TITLE OF EDUCATIONAL ACTIVITY (ARTICLE)**

Drug Treatment of the Complications of Refractive Surgery:  
LASIK, LASEK and PRK

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. Laser in-situ keratomileusis (LASIK), photorefractive keratectomy (PRK) and laser sub-epithelial keratomileusis (LASEK) are types of refractive surgery that:
  - a) sculpt the epithelial surface of the cornea.
  - b) recontour the epithelial surface of the iris.
  - c) permanently ablate predetermined portions of the stromal layer of the cornea.
  - d) smooth the surface of the retina.
2. LASIK surgery:
  - a) is the recommended refractive surgery for patients with myopia with thin corneas.
  - b) involves the complete removal of the epithelial layer of the cornea.
  - c) is currently the only refractive surgery that utilizes the excimer laser.
  - d) may correct myopia, hyperopia and astigmatism.
3. Diffuse lamellar keratitis:
  - a) is an infection of the cornea.
  - b) is more commonly associated with LASIK surgery.
  - c) is more commonly associated with LASEK surgery.
  - d) is typically a result of *Mycobacterium chelonae* infection.
4. If post-operative infectious keratitis is suspected:
  - a) corticosteroid eye drops should be started immediately.
  - b) gram-positive bacteria are likely the causative organisms.
  - c) keratoplasty is often the ultimate treatment.
  - d) the corneal flap should not be moved.
5. A person with myopia:
  - a) may also be referred to as farsighted.
  - b) has a focal point that lands behind the retina.
  - c) has a focal point that lands in front of the retina.
  - d) sees objects at a distance more clearly than objects nearby.
6. Post-operative infectious keratitis:
  - a) is a complication unique to LASIK.
  - b) is a complication unique to PRK because the corneal epithelium is completely removed.
  - c) is a common complication of refractive surgeries in general.
  - d) may occur as early as the first week to several months post-operatively.

7. *Mycobacterium chelonae* keratitis:
  - a) has been reported to typically occur during the first week post-operatively.
  - b) has not been documented.
  - c) typically appears more than 10 days post-operatively.
  - d) is best treated by starting topical corticosteroids.
8. During LASEK:
  - a) the epithelial layer of the cornea is broken down by applying 18-20% ethanol.
  - b) the epithelial layer of the cornea is undisturbed.
  - c) the epithelial layer of the cornea is broken down by applying 10-12% ethanol.
  - d) the epithelial layer of the cornea is completely removed.
9. Generally, more severe visual problems have been noted in cases of:
  - a) fungal keratitis.
  - b) *Staphylococcus aureus* keratitis.
  - c) *Staphylococcus epidermidis* keratitis.
  - d) asymptomatic keratitis.
10. Diffuse lamellar keratitis has been reported to occur in:
  - a) 0.2-3% LASIK patients.
  - b) 3% of patients with blue eyes.
  - c) 1-2% of LASEK patients.
  - d) 3-4% of PRK patients.

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

**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.

# New Molecular Entities & Biologicals

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

*FDA Approvals*  
January – March 2005

## *Evidence of Safety and Efficacy*

### Entecavir

*Baraclude*™ Tablet,  
Bristol Myers Squibb

Lai CL, Rosmawati M, Lao J, Van Vlierberghe H, et al. **Entecavir** is superior to lamivudine in reducing hepatitis B virus DNA in patients with chronic hepatitis B infection. *Gastroenterology*. 2002; 123:1831-1838. (*IDIS* Article Number 492287)

Approved 29Mar2005  
for treatment of chronic  
hepatitis B infection

This multicenter, phase II randomized trial of 169 patients with chronic hepatitis B virus (HBV) infection, compared the safety and efficacy of oral entecavir 0.01 mg/day, 0.1 mg/day or 0.5 mg/day to oral lamivudine 100 mg/day and found that entecavir was well tolerated and reduced HBV DNA an additional 0.97 log<sub>10</sub> at the 0.1 mg/day dose and an additional 1.28 log<sub>10</sub> at the 0.5 mg/day dose (p<0.0001) compared with lamivudine.

#### *IDIS Search Terms [15 IDIS citations]*

Entecavir	8180032
Hepatitis, Viral B	070.2

### Micafungin Sodium

*Mycamine*™  
Intravenous Infusion,  
Fujisawa

Hiemenz J, Cagnoni P, Simpson D, Devine S, et al. Pharmacokinetic and maximum tolerated dose study of **micafungin** in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. *Antimicrob Agts Chemother*. 2005; 49: 1331-1336. (*IDIS* Article Number 531898)

Approved  
16Mar2005 for  
prophylaxis of  
Candida infections in  
stem cell transplant  
patients and  
treatment of  
esophageal  
candidiasis

In a randomized, double-blind dose escalation study, with a total of 86 cancer patients undergoing bone marrow or peripheral blood stem cell transplant, given up to 4 weeks of fluconazole 400 mg/day and either normal saline (control) or micafungin 12.5 to 200 mg/day, investigators found that the area under the curve for micafungin was proportional to the dose and the half-life was about 13 hours, consistent with the micafungin pharmacokinetic profile in healthy volunteers. Investigators also found that 5 of 12 patients (42%) who received fluconazole alone, and 14 of 62 (23%) of patients who received fluconazole with micafungin, had a suspected fungal infection during treatment, while the maximum tolerated dose for micafungin was not reached, even at 200 mg/day.

Pawlitz D, Young M, Klepser M. **Micafungin**, a new echinocandin antifungal. *Formulary*. 2003; 38:354-367 (*IDIS* Article Number 500332)

This comprehensive review included the chemistry, pharmacology, and spectrum of activity of micafungin, as well as special patient considerations, dosing, drug interactions and adverse events. Pharmacokinetic information from several clinical studies was also presented.

#### *IDIS Search Terms [9 IDIS citations]*

Micafungin	8120420
Candidiasis, Esophagus	112.84
Candidiasis NEC	112.

## Pramlintide Acetate

Symlyn™ Injection,  
Amylin

Hollander PA, Levy P, Fineman MS, Maggs DG, et al. **Pramlintide** as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes. *Diabetes Care*. 2003; 26:764-790. (IDIS Article Number 517795)

Approved  
16Mar2005 in  
conjunction with  
insulin to treat  
diabetes

In this year-long randomized, placebo-controlled multicenter study of 656 patients with type 2 diabetes who received subcutaneous injections of pramlintide, 60 mcg TID, 90 mcg BID or 120 mcg BID or placebo in addition to insulin therapy, investigators found that pramlintide 120 mcg BID resulted in a sustained reduction from baseline HbA<sub>1c</sub> of 0.68% at 26 weeks and 0.62% at 52 weeks which was significantly more than seen with placebo (p<0.05). The proportion of patients who reached an HbA<sub>1c</sub> <8% was about twofold greater in those who received pramlintide 120 mcg/day (46%) than with placebo (28%) (p<0.05).

Whitehouse F, Kruger DF, Fineman M, Shen L, et al. A randomized study and open-label extension evaluating the long-term efficacy of **pramlintide** as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care*. 2002; 25:724-730. (IDIS Article Number 479246)

In a multicenter, randomized, placebo-controlled, 52-week study 480 type 1 diabetes patients received subcutaneous injections of placebo or pramlintide at doses of 30 mcg 4 times a day in addition to their insulin therapy, and pramlintide treated patients were re-randomized at week 20 to 30 or 60 mcg 4 times daily if at week 13 the HbA<sub>1c</sub> had decreased less than 1% from baseline. Investigators found that at week 13 pramlintide treatment resulted in a mean reduction of HbA<sub>1c</sub> from baseline of 0.67% which was significantly greater than the 0.16% reduction in the placebo group (p<0.0001), and further found that a significant treatment effect was carried through to 52 weeks (p<0.0071).

### **IDIS Search Terms [15 IDIS citations]**

Pramlintide	68200011
Diabetes Mellitus	250.

### About the author

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# Safety of sulfonylurea use in type 2 diabetic patients with coronary artery disease during periods of myocardial ischemia. . .is there a problem?

Perspective from an



IDIS Subscriber

## Patient

RR is a 60-year-old retired white male, with a 25 year history of hypertension, and a 15 year history of hyperlipidemia and type 2 diabetes mellitus (T2DM). He is 73 inches tall and obese with a body mass index of 31 kg/m<sup>2</sup>. He had a myocardial infarction 15 years ago. He has no history of significant renal or hepatic disease. His family history is positive for coronary artery disease with several maternal uncles who died after myocardial infarctions in their 50's or 60's. His current medications include: metformin 850 mg twice daily, rosiglitazone 4 mg daily, rosuvastatin 10 mg daily, lisinopril 20 mg twice daily, hydrochlorothiazide 12.5 mg twice daily, atenolol 100 mg daily, and aspirin 81mg daily. Laboratory values on the day of admission included: sodium 140 mEq/L, potassium 4.4 mEq/L, BUN 19 mg/dl, creatinine 1.6 mg/dL, liver functions tests within reference range, high-density lipoprotein cholesterol 40 mg/dL, low-density lipoprotein cholesterol 105 mg/dL, triglycerides 170 mg/dL, HbA<sub>1c</sub> 8.1 %. Vital signs on admission included: pulse rate 60, respiratory rate 18, T 98.8F, BP 118/75 mm/Hg. RR had been in his usual state of health until several days prior to admission, when he noticed new onset chest pain on exertion. On the morning of admission he again reported chest pain on exertion. He called his family practice physician who instructed him to report to the ER to be worked up for acute coronary syndrome. ER staff admitted him to medicine service. The admitting physician decided to hold RR's metformin pending the need for invasive studies requiring contrast. He then started glyburide 5 mg daily in its place. All RR's other medications were to be continued.

## Background

Unlike the studies that led to the discovery of insulin, the hypoglycemic effect of the sulfonylureas was discovered accidentally by Janbon and colleagues<sup>1</sup>, who reported the hypoglycemic effect of sulfonamides used to treat typhoid fever. Over the next decade a number of effective compounds were synthesized and introduced into clinical practice.<sup>2</sup> By the 1960s sulfonylureas were popular with physicians and patients and widely used in the treatment of T2DM. They allowed patients to lower their blood sugar without insulin injections and to avoid the unpopular diets often prescribed for overweight diabetics.

The University Group Diabetic Program (UGDP)<sup>3</sup> began in the United States in 1961 as the largest and best-designed clinical trial in the world at that time. Its purpose was to determine: What is the value of

lowering blood sugar in T2DM? Are oral sulfonylurea drugs a safe and effective way of lowering blood sugar? Unfortunately the normal publication of results was pre-empted by a *Wall Street Journal* report that large numbers of diabetics were being killed by the antidiabetic drug tolbutamide (Orinase®). The subsequent controversy did little to endear the drug or future UGDP publications to the average physician. When the results of UGDP were published, they included a substantially increased risk of cardiovascular mortality in the tolbutamide group versus the insulin groups or the diet group.<sup>4</sup> After the publication of the UGDP report the use of tolbutamide declined. The FDA quickly endorsed the UGDP conclusion that tolbutamide might be dangerous and decided to put warning labels on all sulfonylurea drugs. Court

challenges delayed the implementation of the warning about possible cardiovascular risk associated with sulfonylureas for at least a decade. The warning finally was added in the early 1980's and is unchanged to the present time. Several discussions of the UGDP controversy are available for the interested reader.<sup>5,6,7</sup>

Subsequently, several smaller randomized studies of tolbutamide in T2DM patients did not report any adverse cardiovascular effects.<sup>6</sup> By the late 1970s, either because the UGDP results were not confirmed or the patients' and physicians' desire to avoid insulin therapy, or both, sulfonylurea use had greatly increased. Today sulfonylureas are the preferred class of oral antihyperglycemic drugs. Their popularity is based on familiarity, once daily dosing, effectiveness in recently diagnosed patients, lack of

symptomatic side effects except hypoglycemia, and their low cost.

## **New discoveries in the 1980s prompt re-examination of possible sulfonylurea cardiac toxicity**

In 1983, the adenosine triphosphate-sensitive potassium [ $K_{ATP}$ ] channel was discovered and it was determined that sulfonamides and sulfonylureas block the opening of this channel.<sup>8</sup>  $K_{ATP}$  channel blocking is the mechanism of action of sulfonylureas in the beta cell of the pancreas.  $K_{ATP}$  channels also occur in myocardial cells. Sulfonylureas also bind to cardiac  $K_{ATP}$  channels in the heart. They may also block the opening of the  $K_{ATP}$  channels in the heart under ischemic conditions. These channels are activated by low adenosine triphosphate (ATP) levels and inhibited by high ATP levels. Opening the  $K_{ATP}$  channel has a protective effect in the heart. Blocking  $K_{ATP}$  channels inhibits vasodilatation in response to ischemia or hypoxia.

A few years later in 1986, a form of endogenous protection against myocardial infarction, now known as ischemic preconditioning (IP), was described in a canine model after sublethal episodes of ischemia.<sup>9</sup> In a recent editorial, IP is described as reproducible in all mammalian species studied, not dependent on collateral coronary circulation, capable of reducing infarct size by as much as 70%, decreasing arrhythmias, and eliminating ST-segment elevation.<sup>10</sup> IP has now been demonstrated in isolated human myocardial tissue.<sup>11</sup>

## **Evidence for ischemic preconditioning in humans**

Tomai and colleagues<sup>12</sup> have recently reviewed the clinical implications of human IP. Obviously human trials to directly demonstrate IP are not possible. However, evidence of human IP has been described in percutaneous coronary intervention,<sup>13</sup> after angioplasty for acute myocardial infarction,<sup>14</sup> and in coronary angioplasty patients.<sup>15</sup> Leesar and colleagues<sup>16</sup> have

recently demonstrated that both ischemic and adenosine types of preconditioning exist in humans during percutaneous transluminal coronary angioplasty (PTCA). The intracoronary infusion of 20 mg of adenosine over 10 minutes resulted in elimination of any difference in chest pain, elimination of any difference in the ST-segment shift, or lactate extraction ratio between the first, second, and third balloon inflations. Their data support the proposition that either brief ischemic episodes associated with standard PTCA or pharmacologic preconditioning with adenosine result in IP.

Lee and Chou<sup>17</sup> studied the effect of single doses of glyburide 10 mg or glimepiride 2 mg 1 hour before catheterization on IP in non-diabetic patients and diabetic patients undergoing PTCA. In the non-diabetic group, chest pain was significantly less during the second inflation than the first inflation consistent with effective IP. In patients pretreated with glyburide, chest pain was significantly increased after the second inflation, in comparison with the both control and glimepiride treated groups, consistent with reduced or ineffective IP. In the group treated with both glyburide and nicorandil ( $K_{ATP}$  channel opener), chest pain after the second inflation was significantly improved compared to the group treated with only glyburide, consistent with the possibility that opening of the  $K_{ATP}$  channels provides the cardioprotective effect. Their results suggest a lack of IP protection in diabetic hearts and the different effect of glyburide and glimepiride on IP. Either acute loading or the long term use of glyburide abolished IP in their subjects. They suggest that glimepiride does not block  $K_{ATP}$  channels. If it is confirmed that glimepiride does not block  $K_{ATP}$  channels, it would be preferred for use in T2DM patients.

## **Recent editorial comment**

Within the past 2 years at least 4 editorials have addressed this topic.<sup>10,18,19,20</sup> Miura<sup>18</sup> suggests that autonomic diabetic neuropathy may prevent ischemia from activating receptors relevant to IP. He adds that it is possible that sulfonylureas blocked cardiac  $K_{ATP}$  channels in some diabetic patients preventing IP.

Brady and Jovanovic<sup>19</sup> are concerned that sulfonylurea drugs lower the

magnitude of ST-segment elevation in patients presenting with acute myocardial infarction leading to less use of thrombolytic therapy. If the new ideas of IP in humans and blockade of IP by sulfonylureas are correct, it would seem reasonable to find diminished clinical outcomes after sulfonylurea use in T2DM patients similar to the UGDP data. The United Kingdom Prospective Diabetes Study Group (UKPDS) followed 3,867 newly diagnosed T2DM patients who were randomly assigned to intensive treatment with a sulfonylurea, insulin, or conventional treatment. Over a 10 year period the use of sulfonylureas was not associated with increased mortality. However, none of the patients enrolled in UKPDS were over 65-years-old or had a history of cardiac disease. On the other hand, in diabetics undergoing angioplasty for acute myocardial infarction, the risk of death was found to be 2.77 times higher in 67 T2DM patients taking sulfonylureas than in 118 T2DM patients not taking them. In all patients with successful revascularization long-term outcome was not impacted by sulfonylurea use.<sup>14</sup> They conclude the consequences of sulfonylurea use is apparently determined by the presence or absence of myocardial ischemia. They recommend that any patient who presents with a suspected acute coronary syndrome, who is on a sulfonylurea, should immediately have the sulfonylurea discontinued and have insulin substituted when necessary. They consider the sulfonylurea controversy still unresolved.

Riddle<sup>20</sup>, the only endocrinologist commenting on the topic, notes the recent reports indicating that glyburide can impair IP in patients without T2DM, and in patients with T2DM. He reminds us that even if glyburide impairs IP, it may have other beneficial effects such as improvement in glycemic control which are more important than the problems with IP. He concludes that the available

evidence supports not only avoiding glyburide in hospital, but replacing oral therapy with insulin on hospitalization.

## Comment

In this case, a patient with known coronary artery disease, admitted to rule out ACS, I would like to avoid sulfonamide or sulfonylurea use. Although there are no trials, practice guidelines, or consensus expert opinions, the demonstrated problems with even single doses of sulfonylureas in the setting of acute myocardial infarction, angioplasty, and PCI are impressive. The recent findings from the UKPDS trial cannot simply be applied to patients with significant ischemia or hypoxemia. Since the insulin alternative is available for in hospital use, avoiding the sulfonylurea is the most conservative choice. If a sulfonylurea is to be started, glimepiride is the only agent shown not to affect IP.

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From time to time, we publish articles contributed by IDIS subscribers. An article from Dave Mace, B.S.Pharm., is included in this issue. Dave Mace is from an institution that is a long-standing IDIS subscriber, utilizing the database on a regular basis. His ARTICLE illustrates IDIS database use contributing directly to patient care outcomes. The responsibility for errors is the author's alone. The ARTICLE does not necessarily represent hospital views and recommendations. We hope you find the information interesting and useful. We welcome comments. If you are interested in sharing your experiences using the IDIS database, please contact donna-brus@uiowa.edu

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