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Use of onabotulinumtoxinA for overactive bladder with concomitant warfarin

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Abstract

Overactive bladder symptoms (OAB) can be treated with oral medications using a variety of antimuscarinic medications and more recently mirabegron, a beta-3 agonist. However, the use of these medications may be limited for patients due to adverse drug reactions, contraindications, and those who are refractory to oral medications. Recently, intravesical injections of onabotulinumtoxinA (onaBoNTA) have been proven to be safe and effective as an alternative to oral OAB medications. Although this procedure is typically thought to be outside the realm of a consultant pharmacist, there are incidences in which a pharmacist can make a substantial impact on patient care.

The patient, a 71 year old female, presents to her urologist for evaluation to assess appropriateness of intravesical onaBoNTA injections. She has failed multiple oral medications for the treatment of her OAB with urge incontinence. The procedure is further complicated by the patient's past medical history of atrial fibrillation, deep vein thrombosis, and pulmonary embolism which requires anticoagulation with warfarin therapy.

This case demonstrates the use of onaBoNTA for OAB in a patient concomitantly receiving warfarin for atrial fibrillation, pulmonary embolism, and deep vein thrombosis. Specifically, it demonstrates discontinuation, bridge therapy, and reinitiation of warfarin on a patient undergoing intravesical injections of onaBoNTA for OAB along with a collaborative approach to care with a pharmacist and urologist.

Keywords

Overactive bladder; warfarin; onabotulinumtoxinA; low-molecular weight heparin

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Introduction

Overactive bladder (OAB) is a urological condition defined by the presence of urinary urgency (a compelling need to urinate which is difficult to avoid), increased frequency (eight or more micturitions per waking hours), and nocturia (awakening to urinate one or more times per night), with or without urinary incontinence.^{1–3} The prevalence of OAB increases with age, disproportionately affecting older adults.^{4–6}

The primary pharmacological treatments for OAB are antimuscarinic medications includes oxybutynin, which was approved for OAB in 1975 by the Food and Drug Administration (FDA), along with several other antimuscarinic chemical moieties or the beta-3 agonist mirabegron, which was FDA approved for OAB in 2012.^{1,7} These medications have been proven to be effective; however, utility may be limited, especially in the elderly, due to adverse drug events (ADEs). Antimuscarinics can cause dry mouth, constipation, and dry eyes along with confusion in older adults.^{8–10} Additionally, antimuscarinics should be used with caution in patients with urinary retention, decreased gastrointestinal motility, and glaucoma. Mirabegron has also been linked to an increase in blood pressure and heart rate.¹¹

There are populations of patients who are treatment-refractory, cannot tolerate, and/or unable to utilize antimuscarinics or beta-3 agonists due to comorbid conditions.¹² For these patients the use of onabotulinumtoxinA (onaBoNTA) has been proven safe and effective.¹³ OnaBoNTA was approved by the FDA for the treatment of OAB in January 2013.¹⁴ OnaBoNTA is administered via intravesical injections into several locations of the detrusor, the muscle of the bladder, under local anesthesia with effects typically lasting for twelve weeks.^{12–13}

In most cases, this procedure does not warrant intervention by a consultant pharmacist. However, certain comorbid conditions may require a pharmacist's clinical expertise. We aim to discuss a patient currently using warfarin who is recommended to be initiated on intravesical onaBoNTA.

Case presentation

The patient, a 71 year old female, has a two year history of OAB with urge-incontinence. She has failed multiple oral medication agents including oxybutynin and fesoterodine and currently remains dependent on pads and absorptive underwear. The patient presents to her urologist for evaluation to assess appropriateness of intravesical onaBoNTA injections. During this clinic visit, her physical findings include a weight of 102 kilograms (kg), a height of 63 inches and body-mass index (BMI) of 39.8 kg/m², and vitals that include blood pressure (BP) 142/70 mmHg and heart rate of 65 beats/minute. Due to her warfarin therapy, her urologist consults the pharmacist managed anticoagulation clinic for the development of a therapeutic and monitoring plan for the patient's anticoagulation therapy prior to undergoing the onaBoNTA procedure.

Past Medical History

The patient was diagnosed with OAB approximately two years prior to this presentation to her urologist's office and has failed two oral antimuscarinics. Her current past medical history is also significant for coronary artery disease, hypertension, hyperlipidemia, type 2 diabetes mellitus, urinary tract infection, angina, atrial fibrillation, deep vein thrombosis (5/2004), and pulmonary embolism (8/2008).

Laboratory Findings

The most current laboratory values prior to visiting her urologist are significant for:

INR (International normalized ratio): 2.14

Sodium: 144 mEq/L

Potassium: 4.9 mEq/L

Serum creatinine: 0.86 mg/dL

Total cholesterol: 172 mg/dL

Triglycerides: 113 mg/dL

High-density lipoprotein: 59 mg/dL

Low-density lipoprotein: 90.4 mg/dL

Hemoglobin: 11.2 g/dL

Hematocrit: 35.3%

Glucose: 98 mg/dL

Hemoglobin A1c: 6.0%

At the urologist's office a urine culture was ordered prior to the procedure. The culture revealed pansensitive *Escherichia coli*; treatment was initiated upon receiving results.

Current Medications

Losartan 50 mg: 1 tablet by mouth daily for hypertension

Amlodipine 10 mg: 1 tablet by mouth daily for hypertension

Furosemide 20 mg: 1 tablet by mouth daily for hypertension

Metformin 500 mg: one-half tablet by mouth twice a day for diabetes

Niacin 500 mg: 2 tablets by mouth at bedtime for hyperlipidemia

Metoprolol tartrate 50 mg: 1 tablet by mouth twice a day for hypertension

Nitroglycerin 0.4 mg: 1 sublingual tablet every 5 minutes as needed for chest pain

Clopidogrel 75 mg: 1 tablet by mouth daily for stroke prevention

Warfarin 2 mg: 4 tablets by mouth daily (total daily dose 8mg) indefinitely for atrial fibrillation and history of deep vein thrombosis and pulmonary embolism

Ciprofloxacin 500 mg: 1 tablet by mouth twice a day for positive urine culture (*E. coli*) for 7 days

Allergies

Naproxen – rash

Sulfa – erythema

Statins – myalgias

Lisinopril – cough

Codeine – pruritus

Erythromycin – rash

Pentazocin – nausea and vomiting

Medication Related Problems

Efficacy of OnabotulinumtoxinA

For several years, only studies of onaBoNTA with relatively small enrollees were evaluated (ranging from 14 to 74 subjects) for OAB.¹³ In 2011 these results were compiled in a Cochrane review, which evaluated 19 studies prior to February 2010 and showed that the use of onaBoNTA was superior to placebo in incontinence episodes and urinary frequency. Since this published Cochrane review, larger studies have replicated the efficacy of onaBoNTA over placebo.^{15–22} These studies ranged from 76 to 387 subjects using doses of onaBoNTA ranging from 50 – 300 units per procedure.

Adverse effects of OnabotulinumtoxinA

Adverse effects concerns did arise from these studies; these reports included urinary tract infections, elevated postvoid residual volumes, voiding difficulty requiring intermittent self-catheterization, and bleeding.^{15–21} Hematuria occurred in 3.6 to 5.2% patients and may be of concern to patients using anticoagulant therapy such as warfarin or aspirin.^{20–21}

OnabotulinumtoxinA and warfarin

Currently there are no studies or published guidelines available describing the concomitant use of onaBoNTA and anticoagulants such as warfarin. Due to the risk of bleeding, subjects in onaBoNTA trials treated with an anticoagulant were either excluded¹⁶ or had the anticoagulant discontinued for one week prior to the administration of onaBoNTA.²³ Neither studies nor published guidelines state when reinitiation of anticoagulant is recommended to occur; moreover, based on the indication for anticoagulation, other measures beyond simply holding warfarin dosing for one week should be considered.

Pharmacists Intervention

After the patient's consultation with her urologist, the pharmacist managed anticoagulation clinic was notified of the upcoming onaBoNTA procedure and was consulted to prepare for a treatment strategy. Her current warfarin dose is 8 mg daily (42mg per week); her most

recent INR is 2.14 which is within the INR goal range of 2 – 3.²⁴ Upon discussions with the urologist and incorporating her past medical history, the anticoagulation clinic developed a specific therapeutic regimen for her treatment schedule, monitoring (INR follow-up), and warfarin and enoxaparin dosing.

Due to the patient's extensive history of thromboembolic events and atrial fibrillation, with a CHADS₂ score of two, the pharmacist managed anticoagulation clinic decided to provide bridge therapy for this patient.^{24–25} The treatment plan was to hold warfarin therapy for seven days prior to the procedure instead of the standard five days based on a study done by Kuo, along with discussions with the urologist. The intravesical onaBoNTA procedure was categorized as low-risk while the patient was classified as a high thromboembolic risk based on her past medical history.

The patient was educated to hold the warfarin dose starting seven days prior to the procedure. She was also initiated on a therapeutic dose of enoxaparin, 100mg (1mg/kg) subcutaneous twice a day, seven days prior to the procedure and was then held 24 hours prior to the procedure. Both enoxaparin and warfarin were restarted 24 hours after onaBoNTA was successfully administered. A follow-up appointment was scheduled for INR evaluation 5 days after the procedure to monitor anticoagulation to assess the need for continued enoxaparin. Six days after the procedure, her INR was 1.9 so warfarin 8mg daily and enoxaparin 100mg subcutaneously twice a day were both continued and another follow-up INR was scheduled 5 days later. Her INR was 2.4, 11 days post-procedure; warfarin therapy was continued and enoxaparin was discontinued at this time. A follow-up appointment was scheduled to reevaluate her INR in 10 days which resulted in an INR of 2.6; warfarin therapy was continued unchanged and normal INR monitoring resumed.

Discussion

OnabotulinumtoxinA

As noted above, many studies have proven onaBoNTA to be safe and effective in the treatment of OAB, but until recently, there has not been a comparison to the standard of care: antimuscarinics. The Anticholinergic versus Botulinum toxin Comparison (ABC) study was a double-blind and double placebo controlled 6-month trial in which subjects received either onaBoNTA 100 units plus oral placebo (n=122) or solifenacin 5mg by mouth daily (which could be increased to 10mg daily or switched to trospium XR 60mg by mouth daily) plus intravesical saline injections (n=127).²⁶ After six months, there was a reduction from baseline urge incontinence episodes per day for both onaBoNTA (–3.3) and antimuscarinic therapy (–3.4) with no difference between treatment arms ($p=0.81$). Additionally, there was no difference between groups based on previous antimuscarinic use ($p=0.16$) or baseline frequency ($p=0.53$). When the onaBoNTA arm was compared to the antimuscarinics treatment arm, there was a significant increase in complete resolution of urgency urinary incontinence (27% vs. 13%, $p=0.003$) and complete resolution in all incontinence (23% vs. 11%, $p=0.003$), respectively. In terms of ADEs, there was an increased incidence of dry mouth in the antimuscarinic group compared to the onaBoNTA group (46% vs. 31%, $p=0.02$). Moreover, there was an increased risk for urinary tract

infection in the onaBoNTA group compared to the antimuscarinic group (33% vs. 13%, $p<0.001$).

Along with subjective improvements in OAB symptoms, data has proven that patients are satisfied with the use of onaBoNTA even though it requires a procedural intervention. The use of the modified overactive bladder patient satisfaction with treatment questionnaire (OAB-PSTQ) has been evaluated.²⁷ This Likert-scale assessment consists of 12 validated and 4 non-validated questions evaluating the impact of symptoms and the effects on daily activities, freedom, relationship, and cost. There was a significant improvement in satisfaction from baseline in all treatment groups from week 4 to week 36 ($p<0.05$) and significant improvements compared to placebo in doses of 200 units or higher. Health-related quality of life (HRQL) assessments have also been assessed.²⁸ The urogenital distress inventory (UDI-6), incontinence impact questionnaire (IIQ-7), and EuroQOL-5D (EQ-5D) were used to evaluate HRQL in subjects with idiopathic and neurogenic detrusor overactivity. The UDI-6 evaluates the type of symptom and the degree of bothersomeness, the IIQ-7 measures the amount of urine leakage against quality of life (QOL), and the EQ-5D measures effects on mobility, self-care, usual activities, pain/discomfort, and anxiety depression. Utilization of onaBoNTA showed improvements in UDI-6 and IIQ-7 with no improvements in EQ-5D except for depression/anxiety.

In a pharmacoeconomic analysis, it was noted that the use of onaBoNTA was more costly than antimuscarinic treatment; however, costs were offset by nonresponder costs, additional physician costs, and antimuscarinic medications.²⁹ Additionally, use of onaBoNTA reduced urinary incontinence episodes by approximately 400 per person-year resulting in \$4 per episode in avoided costs when compared to best supportive care.²⁹

OnabotulinumtoxinA use with Warfarin

There is a current void in the literature pertaining to concomitant use of onaBoNTA and warfarin, including guidance in bridge therapy when required. This void has created a therapeutic area which requires practitioners to use guidelines and literature to make an educated inference for each individual patient scenario. The main questions that need to be addressed in a patient scenario involving concomitant use of onaBoNTA injections and anticoagulation therapy with warfarin include: 1) is bridge therapy necessary? 2) what is the patient's thromboembolic risk? 3) how is the procedure classified? 4) when should warfarin therapy be held and restarted? 5) when should enoxaparin be started and discontinued? 6) when should the next INR be scheduled post-procedure? These are all essential questions that should be addressed in the clinical scenario by the pharmacist and other members of the medical team.

The requirement for bridge therapy is based on the type and location of the procedure, along with the thromboembolic risk of the patient. Examples of low-risk procedures include laparoscopic cholecystectomy, appendectomy, and transurethral prostatectomy; high-risk procedures include open-abdominal and open-pelvic procedures. Intravesical injections of onaBoNTA can be classified as low-risk based on the location and invasiveness of the procedure based on the similarity to other low risk procedures.³⁰ A current risk assessment tool is available to evaluate a non-orthopedic surgical patient's thromboembolic risk include

the Caprini Venous Thromboembolism Risk Factor Assessment tool.³¹ At the time of presentation, this patient's thromboembolic risk score using the Caprini tool classified her at highest-risk for venous thromboembolism (Table 1).³¹ Based on this, it is recommended to use pharmacologic prophylaxis with low molecule weight heparin (LWMH).³¹,

The perioperative management of warfarin therapy includes holding warfarin at least five days prior to surgery and restarting warfarin therapy 12 – 24 hours after the procedure.³² In a study conducted by Kuo, the methods indicated that anticoagulation therapy was held for seven days prior to intravesical injections of onabotulinum toxin A (onabotA).²³ When using a therapeutic dose of LMWH for perioperative bridge therapy, LMWH should be initiated when warfarin is held, the dose is held 24 hours prior to the procedure, and both LMWH and warfarin are restarted within 24 hours after procedure. The follow-up appointment for obtaining the next INR should be scheduled 5 – 7 days after the procedure and LMWH therapy can be discontinued once a therapeutic INR is achieved.³²

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Abbreviations

ABC	Anticholinergic versus Botulinum toxin Comparison
ADEs	Adverse drug events
BP	blood pressure
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
DVT	deep vein thrombosis
EQ-5D	EuroQOL-5D
FDA	Food and Drug Administration
HIT	heparin-induced thrombocytopenia
IBD	irritable bowel disease
IIQ- 7	Incontinence impact questionnaire
INR	International normalized ratio
KG	kilogram
MI	myocardial infarction
MG	milligram
OAB	Overactive bladder
OAB-PSTQ	Overactive bladder patient satisfaction with treatment questionnaire

OnaBoNTA	OnabotulinumtoxinA
PE	pulmonary embolism
PNA	pneumonia
QALYs	Quality adjusted life-years
QOL	Quality of life
LMWH	Low molecular weight heparin
UDI-6	Urogenital distress inventory

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Summary

Patients unable to be treated by conventional therapy may have a reduced quality of life due to untreated symptoms of OAB. After evaluation by a urologist or other qualified medical personnel, the utilization of onaBoNTA may be considered as an FDA approved medication used to mitigate these symptoms. Additionally, patient's utilizing anticoagulation therapy should be evaluated on a case-by-case basis, to determine a risk for a thromboembolic event and need for appropriate bridge therapy.

The pharmacist has an integral role in this patient's care due to the current use of anticoagulation therapy with warfarin along with the need to provide bridge therapy. The gap in literature requires healthcare professionals to collate the existing information for bridge therapy, communicate interprofessionally, and develop an appropriate, patient-centered regimen. This clinical scenario gives insight to other pharmacists and their potential impact in making recommendations for a patient undergoing an intravesical injection of onaBoNTA procedure for OAB while being treated with warfarin.

Take Home Points

OnabotulinumtoxinA is a safe and effective, FDA approved treatment for OAB in specific patient populations which includes patients with treatment refractory OAB, inability to tolerate or utilize antimuscarinic or beta-3 agonists.

There is a lack of current studies or guideline driven recommendations for formulating bridge therapy regimens for patients undergoing intravesical injections of onaBoNTA.

Developing bridge therapy regimens should be initiated by reviewing existing literature related to bridge therapy, inter-professional communication, and include a patient-centered design.

Monitoring is required for both the anticoagulant effect of warfarin and the need for enoxaparin therapy.

Further study is needed to establish appropriate guidelines.

Table 1

Caprini Venous Thromboembolism Risk Factor Assessment for the Case Patient

Points per Factor	Risk Factors
1 point	☐ Age 41–60 ☐ Minor Surgery Planned ☐ History of Major Surgery (<1 month) ☐ Varicose Veins ☐ History of IBD ☐ Swollen legs (current) ☒ Obesity (BMI >25 kg/m²) ☐ Acute MI ☐ CHF ☐ Sepsis (<1 month) ☐ Serious lung disease (PNA) ☐ COPD ☐ Bed rest ☐ Oral contraceptive or hormone replacement[†] ☐ Pregnancy or postpartum (<1 month)[†] ☐ History of unexplained stillborn infant, recurrent spontaneous abortion (3 or more months), premature birth with toxemia or growth-restricted infant[†]
2 points	☒ Age 60–74 ☐ Arthroscopic surgery ☐ Malignancy ☐ Major surgery (>45 minutes) ☒ Laparoscopic surgery (>45 minutes)[‡] ☐ Patient confined to bed (>72 hours) ☐ Immobilizing plaster cast (<1 month) ☐ Central Venous Access
3 points	☐ Age 75 or older ☒ History of DVT/PE ☐ Family history of thrombosis ☐ Positive Factor V Leiden ☐ Positive Prothrombin 20210A ☐ Elevated serum homocysteine ☐ Positive lupus anticoagulant ☐ Elevated anticardiolipin antibodies ☐ HIT
4 points	☐ Elective major lower extremity arthroplasty ☐ Hip, pelvis, or leg fracture (<1 month) ☐ Stroke (<1 month)

Points per Factor	Risk Factors
	☐ Multiple trauma (<1 month) ☐ Acute spinal cord injury (paralysis <1 month)
Total	8 points

Abbreviations: CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease, DVT = deep vein thrombosis, HIT = heparin-induced thrombocytopenia, IBD = irritable bowel disease, MI = myocardial infarction, PE= pulmonary embolism, PNA = pneumonia

[†] For women only

[‡] Intravesical procedure was classified as a laparoscopic surgery

Total points and Risk Level: 0–1 points (low), 2 points (moderate), 3–4 (high); 5 or more (highest)

Reference= 31 (adapted with permission)