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SHANDS HOSPITAL

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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met November 19, 2013. 3 drugs were added in the *Formulary*, 1 product was deleted, 5 drugs were designated non-formulary and not available, 1 product was designated high-priority non-formulary, and 1 therapeutic interchange was approved.

◆ ADDED

Diphtheria, Tetanus Toxoid, and Acellular Pertussis, Hepatitis B, and Inactivated Poliovirus (Pediarix®)

Hydroxyethyl Starch 6% Solution (Voluven®)*

**Restricted to submucosal injections during endoscopic resection.*

Poractant alfa (Curosurf®)

◆ DELETED

Calfactant (Infasurf®)

◆ NON-FORMULARY AND NOT AVAILABLE

Bupivacaine Liposomal (Exparel®)

Calfactant (Infasurf®)

Etidronate (generic)

Insulin Lispro (Humapen® Luxura™)

Vortioxetine (Brintellix®)

◆ HIGH-PRIORITY NON-FORMULARY

Insulin Glulisine (Apidra®)*

**Restricted to use in insulin pump only.*

◆ THERAPEUTIC INTERCHANGES

Vitamin B Complex Tablet§

§*Interchanged to individual ingredients: thiamine 50 mg, niacin 50 mg, cyano cobalamin 50 mcg, and pyridoxine 50 mg*

(continued on next page)

MEDICATION SAFETY

Re-dosing of reversal agents in the inpatient setting

Antidotes and reversal agents play a critical role in both intentional and unintentional medication overdose. The ideal antidote or reversal agent would completely counteract the unintentional consequences of medication overdose. In a perfect world, this would be achieved via a single dosage of the antidote. However; this is often not the case. A number of agents require intense monitoring post-administration (vital signs, laboratory values, etc.) with potential re-administration necessary to treat continued adverse effects. This article serves to summarize common antidote and reversal agents utilized at UF Health Shands Hospital.

Opioid analgesia is considered a relatively safe treatment option for patients, although sometimes associated with adverse events, the most serious of which is respiratory arrest. The risk of adverse consequences of therapy increases with higher opioid doses, the morbidly obese, pediatric and geriatric populations, critically ill patients, and also those who receive concurrent central nervous and respiratory depressants (such as anxiolytics and sedatives).[1] At the bedside, the most easily recognizable sign of opioid overdose is a decline in respiratory rate. A rate of 12 breaths per minute or less strongly suggests an opioid intoxication, predominantly when the patient is lethargic as well.[2] Naloxone, an antidote for opioid intoxication, is a competitive mu opioid-receptor antagonist which causes a reversal of all signs and symptoms of opioid intoxication. The onset of action of IV naloxone is less than two minutes and has a duration of action of 20 to 90 minutes (a much shorter period of action than that of many opioids). Common opioid elimination half-lives are listed in Table 1. Doses may also be administered intramuscularly, subcutaneously, or orally, but may take up to 15 minutes to work when administered via these alternative routes. The initial dose of naloxone for adults is 0.04-0.4 mg. If there is no response, the dose should then be repeated every two to three minutes. Doses should be initiated low with increases until an adequate level of alertness is achieved. If no response is observed after 10 mg, the respiratory depression is likely not due to opioid intoxication.[3] After naloxone administration, monitor for a reduction in opioid effects in regards to blood pressure, heart rate, and respiratory rate. Naloxone may also precipitate signs and symptoms of opioid withdrawal such as: abdominal cramps, shaking, chills, nausea, vomiting, and diarrhea.[3]

Benzodiazepines (BZDs) are widely prescribed for anxiety in the outpatient setting, but are also used for other indications while patients are in the hospital. Flumazenil is a competitive inhibitor of the gamma aminobutyric acid (GABA) receptor (BZD binding site) and is used to reverse benzodiazepine-related sedation. The classic presentation of BZD overdose manifests as CNS depression with slurred speech, ataxia, and altered mental status with more severe toxicities resulting in lethargy or coma.[5] The recommended dose for sedation reversal is 0.2 mg given IV over 30 seconds. Repeated doses of 0.2 mg up to a maximum single dose of 1 mg administered over 30 seconds may be given at one minute intervals until the desired effect is achieved, with no more than 3 mg of flumazenil given within one hour.[6] The reversal of BZD toxicity occurs rapidly, approximately 6-10 minutes after IV administration. As with naloxone, the duration of the flumazenil is much shorter than many of the agents it is reversing. Many benzodiazepine elimination half-lives are listed in Table 1. In the event of re-sedation, repeated doses may be

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Formulary update, *from page 1*

Diphtheria, Tetanus Toxoid, and Acellular Pertussis, Hepatitis B, and Inactivated Poliovirus (Pediarix®) combination vaccine is indicated for patients at least 6 weeks of age to 6 years of age born to HBsAg negative mothers. The CDC currently recommends vaccination for Hepatitis B, DTaP, Hib, PPSV 23 and IPV at 2, 4, and 6 months of age.

In infants who are born prematurely, it is possible that they would receive their 2, 4 and 6 month vaccinations while in the hospital. This would require 3 needle sticks secondary to lack of a combination vaccine available in the *Formulary*. Historically, UF Health has carried only single entity vaccines due to the wide availability of vaccinations in the outpatient setting.

Evaluation of current practices indicated a potential for decreased needle sticks in infants who remain hospitalized for prolonged periods of time. A cost evaluation was performed which yielded annual cost-avoidance with conversion to the combination vaccination secondary to potential elimination of poliovirus vaccine waste. The Committee voted to add Pediarix® in the *Formulary* while retaining the single-component vaccines for use in patients not requiring the combination series.

Hydroxyethyl Starch 6% (Voluven®) was designated non-formulary and not available in August 2013. The Pharmacy and Therapeutics Committee removed all hydroxyethyl starch (HES) products at that time secondary to a June 2013, FDA-issued MedWatch. This MedWatch noted that intravenous HES should not be used in critically ill adults secondary to increased risk of morbidity, including bleeding and renal injury, as well as mortality. Since that time period, the use of 6% HES for submucosal injection during endoscopic mucosal resection (EMR) was requested by the Department of Gastroenterology. EMR is used to treat precancerous gastrointestinal lesions as well as early malignancies, including laterally spreading tumors in the colonic wall. Historically, 0.9% normal saline in combination with epinephrine has been utilized as submucosal injection to provide a "fluid cushion" for a safe and effective resection.

Recently, data supporting the use of HES for this purpose has emerged with animal studies and 1 small human study showing extended duration of "lift" when HES is used in comparison to normal saline. The data concluded that HES was superior to NS in the provision of an elevated time of mucosal cushion after injection in patients with lesions > 3 cm.

The use of this agent was not requested as a wholesale conversion, but rather for use in patients with lesions greater than 2 cm, with early cancer or high-grade dysplasia (approximately 5 patients per month with expected growth as program expands). At the current rate, this switch will be effectively cost-neutral. The P&T approved addition of this product in the *Formulary* with a restriction to submucosal injection. Intravenous administration of this agent will not be allowed.

Poractant alfa (Curosurf®) was FDA approved in November of 1999 for the treatment (rescue) of respiratory distress syndrome (RDS) in premature infants. It is an extract of natural porcine lung surfactant which consists of 99% polar lipids and 1% hydrophobic low molecular weight proteins (surfactant associated proteins SP-B and SP-C). This agent was requested for addition in the *Formulary* secondary to the supposition that this agent results in a lower incidence of endotracheal tube (ET tube) reflux than our current surfactant product, calfactant.

Administration of any surfactant carries a risk of ET tube occlusion and reflux as well as complete airway obstruction. Product labeling for calfactant indicates it has a 23% incidence of ET tube occlusion/reflux versus no listed incidence with poractant alfa. An open label comparison of poractant to calfactant boasts a statistically significant difference in ET tube occlusion rates (3.5% vs. 13.2% respectively, $p< 0.001$). It has been proposed that administration of calfactant as a continuous infusion via syringe pump may lessen the incidence of reflux into the ET tube.

A cost analysis was performed and showed that when using equivalent dosing (i.e. same number of doses) annual expenditures would be expected to increase approximately $84,000. However, there is limited data that shows that when poractant is utilized, repeat dosing is often unnecessary. Conservative estimates indicate that we could reduce the incidence of re-dosing by about 25% in our NICU population. This would decrease the annual expenditure increase to less than $60,000. Of note, this is only an estimate.

Initial concerns with a switch to poractant included the need to maintain calfactant in the *Formulary* for treatment of meconium aspiration in full term infants (no surfactant product currently carries FDA approval for this indication). However, a study published in China indicated the safety and efficacy of poractant use in full term babies for this indication. The neonatal physician group has indicated approval to use poractant in the full term babies which would eliminate the need to maintain two products in the *Formulary*.

The Committee recommended that poractant be added in the *Formulary* and calfactant be removed and be designated non-formulary and not available. In addition, the Committee recommended that calfactant be retrospectively reviewed for incidence of ET tube occlusion and/or airway occlusion. Poractant would be evaluated for these same adverse outcomes at a 6 month time period.

Bupivacaine Liposomal Injection (Exparel®) was approved by the FDA in October 2011 for single-dose infiltration into the surgical site prior to bunionectomy or hemorrhoidectomy to produce post-surgical anesthesia. In January 2012, the P&T Committee designated bupivacaine liposomal injection non-formulary and not available. The Committee stipulated that this product could be re-evaluated if published literature provided sufficient evidence that it would be cost-effective in the inpatient setting. In August 2013, liposomal bupivacaine was evaluated at the request of The Department of Surgery for use in hemorrhoidectomy and rectal surgeries.

Bupivacaine liposomal injectable suspension is an extended-release formulation of bupivacaine. It works as a local anesthetic whereby upon injection, bupivacaine is released from multivesicular liposomes over time with resultant analgesia up to 72 hours. Bupivacaine exerts its anesthetic effect by blocking the generation and conduction of nerve impulses. This is accomplished through reversible binding to voltage-gated sodium channels which inhibits sodium influx.

An open-label colectomy trial compared multimodal analgesia (bupivacaine liposomal, NSAID and acetaminophen) to an opioid-based analgesia regimen. This was a non-randomized, prospective sequen-

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Formulary update, *from page 2*

tial cohort study which had 39 patients. A reduction of approximately 50% in morphine equivalents (p=0.025), a 26% decrease in hospital cost (p=0.027) and a 59% reduction in median length of stay post-surgery (p=0.004) was noted in the multimodal treatment arm. The authors concluded that these results were both clinically and statistically significant. The clinical significance is debatable as the primary endpoint examined opioid use in two distinctly different treatment arms. Confounders, including the use of NSAIDs and acetaminophen in the multimodal arm compared to liposomal bupivacaine alone, may have altered the reported results.

Another study evaluated hemorrhoidectomy procedures in a randomized, double-blind, parallel phase II active control study. It included 100 patients and compared 75 mg bupivacaine plus epinephrine 1:200,000 to three doses (66 mg, 199 mg and 266 mg) of bupivacaine liposome injection. Statistically significant reductions in mean area under the curve cumulative pain scores from 0-72 hours were noted for the bupivacaine liposome injection 199 mg and 266 mg groups. The authors concluded that these results were both statistically and clinically significant. The sample size of this study, in conjunction with the relatively healthy population makes the generalizability of this study difficult.

Bupivacaine liposome injection is a milky-white substance which creates a risk of medication error in the OR environment due to the potential for confusion between propofol and liposomal bupivacaine. Intravenous injection of the bupivacaine in error would result in a catastrophic event. The Committee felt a formal investigation into the safety of providing this medication to patients in the outpatient OR setting both at UF Health Shands Hospital and Florida Surgical Center was necessary. It was recommended to table the vote for formulary inclusion, and have the Medication Safety Committee perform a Failure Mode and Effects Analysis (FMEA) to outline a procedure for the safe administration of the product if added in the *Formulary*.

The FMEA was conducted and presented to the Committee in November 2013. An adhoc group comprising of members of pharmacy, anesthesia, nursing, risk management, and OR services met to develop a proposal for safe medication administration of liposomal bupivacaine in the OR. The main safety concerns centered around the appearance of the medication and its potential for mix up with propofol as well as an inability to easily identify patients who received the long acting product and ensure they did not receive additional bupivacaine post-operatively.

Limitations in the proposal and potential points of error were discussed and again centered around administration of the drug intravenously in error. Upon presentation of the suggestions as well as limitations, the Medication Safety and Pharmacy and Therapeutics Committee agreed that there were still significant points in the process where human error would potentially occur. The P&T Committees noted that efficacy data did not outweigh the significant safety concerns associated with use of this medication and therefore designated the product non-formulary and not available.

Etidronate is a first generation bisphosphonate which was reviewed for the treatment and prevention of heterotopic ossification (HO) in burn rehabilitation patients. Like other bisphosphonates, etidronate binds hydroxyapatite crystals in bone preventing enzymatic degradation by osteoclasts. Unlike other bisphosphonates, however, etidronate also binds to precursors and prevents the aggregation and formation of hydroxyapatite, thereby reducing mineralization of new bone. This characteristic is believed to be the mechanism by which etidronate prevents the formation of heterotopic bone, or bone that forms inappropriately within soft tissue. Central nervous system injury, total hip arthroplasty, and severe burn injury are events that can precipitate the formation of bone in soft tissue areas surrounding major joints. Etidronate has an FDA approved indication for the treatment of HO following spinal cord injury and total hip arthroplasty.

Etidronate is available generically as 200 mg & 400 mg tablets. Bioavailability is inherently low (~3% of an oral dose) and can be further reduced to negligible levels when the drug is administered with food. Specific administration recommendations must be strictly followed to ensure adequate absorption and to reduce the risk of severe side effects such as esophageal erosion. The recommended dose varies depending on the indication with dosing for the prevention and/or treatment of HO in burn patients not well-defined.

A retrospective cohort study examining all adult patients with 25% or greater total body surface area (TBSA) thermal burns admitted to the Arizona Burn Center over a three-year period evaluated the incidence of HO in burn patients treated prophylactically with etidronate. This was compared to patients who did not receive any prophylactic therapy. The two groups were well matched for age and sex but the etidronate group had significantly greater mean %TBSA involvement (p = 0.03), a characteristic associated with an increased risk of HO development. The results of the study showed that 46.4% of those treated with etidronate developed HO while only 13.8% of the untreated group did (p = 0.01), with all ossification occurring in the elbow. Patient assignment to groups was not randomized – the decision to treat with etidronate was left up to the surgeon. Thus, patients with larger burns and therefore a higher likelihood to develop HO may have been preferentially treated with etidronate (selection bias). However, when %TBSA alone and %TBSA, age, and sex were controlled for via logistic regression, the greater incidence of HO in the treatment group persisted and remained statistically significant (p = 0.004 & 0.03, respectively).

The most commonly observed adverse effects of etidronate in clinical trials were generally mild and involved the gastrointestinal tract. This medication has been associated with fractures when used for extended periods, due to its unique mechanism of action which results in the inhibition of mineralization of developing bone. Post marketing data involving bisphosphonates has revealed serious adverse effects associated with these medications, including esophageal erosion and perforation, which most commonly occur in concert with incorrect medication administration.

Based on the lack of conclusive clinical evidence, serious adverse effects related to incorrect administration, and an elevated cost compared to alternatives, the Committee designated etidronate non-formulary and not available.

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Formulary update, *from page 3*

Insulin Lispro (HumaPen® Luxura™) is a rapid-acting insulin analog commonly used in combination with basal insulin for glucose control in patients with diabetes. From 2000 to 2002, insulin lispro was in the *Formulary* at UF Health Shands Hospital, but it was replaced by the rapid-acting analog insulin aspart in 2002 primarily due to cost considerations. Insulin lispro was reviewed for addition in the Formulary as the HumaPen® Luxura™ device, which allows for dosing in 0.5 unit increments, an important consideration in some pediatric patients. Addition of this insulin/device would allow patients who would utilize this device as an outpatient to be trained on its use prior to discharge.

The efficacy of insulin lispro is well established in adults, adolescents, and children at least 3 years of age. Extensive clinical trial evidence exists showing insulin lispro to be at least as effective as insulin regular in the control of blood glucose in type 1 and type 2 diabetics. Clinical trials in some patient populations have found insulin lispro to be more effective than regular insulin in blunting postprandial spikes in blood glucose. The overall side effect profile of insulin lispro is similar to that of insulin regular, but some studies have associated insulin lispro with a reduced incidence of hypoglycemic events.

With the advent of subsequent rapid-acting analogs, therapeutic equivalence testing was necessary. As a result, head-to-head trials involving insulin lispro, insulin aspart, and insulin glulisine have been conducted and demonstrate similar pharmacokinetic/pharmacodynamic properties, effect on glucose management, and side effect profiles among the agents.

Insulin lispro is available in multiple dosage forms, all with a concentration of 100 units/mL. Dosage forms include 3 mL prefilled KwikPens™, 10 mL vials containing solution for injection, and 3 mL cartridges for use in the HumaPen® Luxura™ administration device. All insulin lispro products are marginally more expensive than insulin aspart products (roughly $5 more for lispro as opposed to aspart). One concern with having an additional insulin product in the *Formulary* is a heightened risk of confusion potentially leading to medication errors.

Based on the immediate availability of insulin aspart as a therapeutic equivalent at our institution (with the availability of 0.5 unit titration with the NovoPen® Junior device), the increased potential for medication errors associated with addition of insulin lispro, and the alternative methods available for training patients before discharge, the Committee designated insulin lispro as non-formulary and not available. It was proposed that UF Health pursue acquisition of HumaPen® Luxura™ training devices such as "dummy pens" if it is desired that patients are trained on that specific device prior to discharge.

Vortioxetine (Brintellix®) inhibits the reuptake of serotonin while antagonizing 5-HT3, 5-HT1D, and 5-HT7 receptors and agonizing 5-HT1A and partially agonizing 5-HT1B receptors. It is approved for once daily administration for the treatment of major depressive disorders. The dose of vortioxetine is 5-20 mg/day without regard to meals. Data indicates vortioxetine may be abruptly discontinued, however, it is proposed that doses of 15-20 mg/day be reduced to 10 mg/day for a week (when possible) prior to full discontinuation.

Vortioxetine is contraindicated with MAO-I agents and should not be used within 14 days of starting or stopping an MAO-I. It should also not be initiated in a patient receiving linezolid or methylene blue. A medication guide is suggested upon initial fill and refill (although not required as part of official REMS). Vortioxetine was designated non-formulary and not available with patients able to take their own medication.

Insulin glulisine (Apidra®) is a rapid-acting insulin product which had previously been unavailable for use at UF Health. Periodically, patients are admitted with an insulin infusing pump containing this rapid-acting insulin. The Pharmacy and Therapeutics Committee recommended allowing patients to utilize their own insulin glulisine when housed within an insulin pump on admission. Patients would not be able to utilize their own glulisine pens or vials while admitted.

It was recommended that insulin glulisine be designated non-formulary, high priority with use restricted to refilling medication in an existing insulin pump. Patients should utilize their supply (already existing in pump upon admission); however, when and if the pump runs dry, the pharmacy would obtain insulin glulisine on a high-priority, non-formulary basis to refill the pump.

Vitamin B Complex orders are often received as admission orders for patients receiving this therapy in the outpatient setting. Currently, this combination product is designated non-formulary and not available. A therapeutic interchange was proposed to allow the conversion to four separate tablets including: thiamine 50 mg, niacin 50 mg, cyanocobalamin 50 mcg, and pyridoxine 50 mg. This interchange will direct prescribers to the appropriate products and allow for automatic conversion in order to satisfy the medication order. This interchange was approved by the Committee.

Reversal agents, *from page 1*

administered at 20 minute intervals as needed with no more than 1 mg given at once, and a max of 3 mg in one hour.[7] After administration of flumazenil, monitor for a return of alertness, reduction in sedation, and the ability to obey commands. The potential for re-sedation is high when used following the administration of long-acting benzodiazepines. Flumazenil administration carries a risk for cardiac arrhythmias and signs/symptoms of benzodiazepine withdrawal (including seizures, hot flashes, tremors, and agitation.)[6]

Therapeutic anticoagulation reduces the risk of thromboembolism, but may place the patient at a higher risk of bleeding. The treatment of clinically significant severe bleeding due to heparin therapy is achieved with neutralization by protamine sulfate. Protamine binds to heparin, forming an inactive complex that is rapidly cleared, normalizing clotting times. Side effects of protamine can include hypotension or bradycardia, which can be minimized by administering protamine slowly. Those who have previously received protamine sulfate-containing insulin (NPH) or those sensitive to fish, are at an increased risk to have previously formed antibodies and experience allergic reactions, including anaphylaxis.[8]

A dose of 1 mg IV protamine will reverse approximately 100 units of heparin remaining in the patient, with a maximum of 50 mg given over 10 minutes.[8] Protamine is cleared from circulation quickly, with a half-life of about 7 minutes.[9] The half-life of IV heparin is 60-90 minutes when given as an infusion, and the amount of heparin received in the previous 2-3 hours is used to calculate the dose of protamine administered. The aPTT should be measured in 5-15 minutes after protamine is given, then again in 2-8 hours to determine the effectiveness and need for re-dosing.

If a low molecular weight heparin (LMWH) has been given within the previous 8 hours, protamine should be given at a dose of 1 mg per 100 anti-Xa units (1 mg enoxaparin equals approximately 100 anti-Xa units).[8] A second dose of 0.5 mg protamine per 100 anti-Xa units should be administered if bleeding continues. Unlike unfractionated heparin, reversal of LMWH is incomplete and difficult to measure.

To reverse the anticoagulation effect of warfarin in patients with clinically significant bleeding, administer vitamin K (phytonadione). The full reversal effect of the INR has been shown to take up to 24 hours, therefore for immediate reversal during serious or life-threatening bleeds, it must be used together with faster-acting agents such as fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC).[10-11] The management of supratherapeutic INRs is detailed in Table 2.

Many of the medications discussed in the article are used daily in practice at UF Health Shands Hospital. This article highlights these agents that potentially require a second administration and the methods used to re-dose these medications in order to return the patient to their previous state.

–Stephanie Worrall, Pharm.D.

REFERENCES

1. Paice JA, Gordon DB, Contreras J, et al. Safe use of opioids in hospitals. Sentinel Event Alert 2012;48:1-5.
2. Boyer EW. Management of Opioid Analgesic Overdose. N Engl. J Med 2012;367:146-55.
3. International Medication Systems, Limited. Naloxone hydrochloride injection package labeling. So. El Monte, Ca 91733. Revised Apr 2012.
4. Barr J, Fraser GL, Puntillo K, et al. Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit. Crit Care Med 2013;41(1):263-306.
5. Weinbroum AA, Flashon R, Sorkine P, et al. A risk-benefit assessment of flumazenil in the management of benzodiazepine overdose. Drug Saf 1997;17:181.
6. Akorn-Strides, LLC. Flumazenil package insert. http://dailymed.nlm.n ih.gov/dailymed/lookup.cfm?setid= 11882e93-aa624d24-895c-6f01d97fc730. Accessed on November 19, 2013.
7. Marraffa JM, Cohen V, Howland MA. Antidotes for toxicological emergencies: A practical review. Am J Health Syst Pharm 2012;69(3):199-212.
8. Garcia DA, Baglin TP, Weitz JI, et al. Parenteral Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e24S-e43S.
9. Ainle FN, Preston RJ, Jenkins, PV, et al. Protamine sulfate down-regulates thrombin generation by inhibiting factor V activation.
10. Ageno W, Gallus A, Wittowsky A, et al. Oral Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl): e44S-e88S.
11. Bauer KA. Reversal of antithrombotic agents. Am J Hematol 2012;87:S119-S126.
12. Guyatt GH, Aki EA, Crowther M, et al. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012

Table 1. The reversal agents and their durations

Medication Class ($t^1/_2$)	Reversal Agent ($t^1/_2$)	Monitor
Opioids[4] ▪ **Fentanyl** (2-4 hours) ▪ **Hydromorphone** (2-3 hours) ▪ **Morphine** (3-4 hours) ▪ **Methadone** (15-60 hours)	**Naloxone**[3] (30-80 minutes)	▪ **Reduction in opioid drug effects:** including respiratory depression, blood pressure, heart rate, and respiratory rate ▪ **Signs and symptoms of opioid withdrawal:** abdominal cramps, rhinorrhea, sialorrhea, anxiety, diaphoresis, shaking chills, gooseflesh of the skin, nausea, vomiting, and diarrhea)
Benzodiazepines[4] ▪ **Midazolam** (3-11 hours) ▪ **Lorazepam** (8-15 hours) ▪ **Diazepam** (20-120 hours)	**Flumazenil**[6] (54 minutes)	▪ Return of alertness, reduction in sedation, the ability to comprehend and obey commands, and improvements in time/space orientation ▪ Re-sedation and respiratory depression, hyptonia, somnolence, areflexia, dizziness, and ataxia ▪ Cardiac arrhythmias (bradycardia or tachycardia) and hypertension may develop ▪ **Signs and symptoms of withdrawal:** seizures, hot flashes, tremors, and agitation
Heparin[8] (1-1.5 hours)	**Protamine**[8] (7 minutes)	▪ Coagulation studies, such as heparin titration test with protamine or plasma thrombin time, that may reveal a need for additional doses ▪ Blood pressure and heart rate
Warfarin[10] (60-72 hours)	**Vitamin K**[10] (1.5-3 hours)	▪ Reduction in bleeding ▪ Prothrombin time/INR for both therapeutic effect and for excess hypoprothrombinemia

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Reversal agents, *from page 5*

Table 2. ACCP recommendations for managing elevated INRs or bleeding in warfarin patients[12]

INR	Management
INR above therapeutic range but < 5; no significant bleeding	▪ Lower dose or omit dose, monitor more frequently, and resume at lower dose when INR is therapeutic ▪ If only minimally above therapeutic range, no dose reduction may be required
INR ≥ 5 but < 9; no significant bleeding	▪ Omit next one or two doses, monitor more frequently and resume at lower dose when INR is in therapeutic range ▪ Alternatively, omit dose and give vitamin K (≤ 5 mg orally), particularly if at increased risk of bleeding ▪ If more rapid reversal is required because the patient requires urgent surgery, vitamin K (2-4 mg orally) can be given with the exception that a reduction of the INR will occur in 24 hours ▪ If the INR is still high, administer an additional 1-2 mg oral vitamin K
INR ≥ 9; no significant bleeding	▪ Hold warfarin therapy and give higher dose of vitamin K (2.5-5 mg orally) with the expectation that the INR will be reduced substantially in 24-48 hours ▪ Monitor more frequently and use additional vitamin K if necessary ▪ Resume therapy at lower dose when INR is therapeutic
Serious bleeding at any elevation of INR	▪ Hold warfarin therapy and vitamin K (10 mg by slow IV infusion), supplemented with fresh frozen plasma (FFP) ▪ Vitamin K can be repeated every 12 hours, if necessary
Life-threatening bleeding	▪ Hold warfarin therapy and give fresh frozen plasma (FFP), supplemented with vitamin K (10 mg by slow IV infusion) ▪ Repeat if necessary, depending on INR ▪ Consider Prothrombin Complex Concentrates