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Must-Know New Drugs

Session Overview

With all of the literature published each year in the various subspecialty areas of emergency medicine, how are we also supposed to stay up to date with the latest medications to hit the market? This session will highlight five must-know new drugs essential for the emergency medicine practitioner.

Objectives

1) Discuss three new agents introduced in 2015 for the reversal of dabigatran, rivaroxaban/apixaban, and non-depolarizing neuromuscular blockers, respectively.
2) List the indications for a new gram-negative antimicrobial.
3) In the setting of an uncontrolled opioid epidemic, evaluate the role of the newest formulation of naloxone to hit the market.

- Reversing anticoagulation - two new products are/will be available for reversing the target-specific anticoagulants dabigatran, apixaban, and rivaroxaban.
    - Idarucizumab
        - The New England Journal of Medicine (Pollack CV Jr, et al. N Eng j Med 2015;373:511-20) and Lancet (Glund S et al, Lancet 2015;386:680-90) both published studies evaluating idarucizumab for reversal of dabigatran. It is a monoclonal antibody fragment that binds dabigatran with high affinity. Dr. Ryan Radecki summarizes the two articles on his EM Lit of Note blog (http://www.emlitofnote.com/2015/06/lets-reverse-dabigatran.html).
        - Here are a few take home points from these early studies:
            - Both studies were funded by Boehringer Ingelheim, who not surprisingly also markets dabigatran. Skepticism is always welcome when the same company makes the drug and the antidote.
            - The Lancet study was conducted in healthy volunteers, while the NEJM study was conducted in patients needing reversal but lacked a control group.
            - Idarucizumab seems to reverse laboratory markers of anticoagulation from dabigatran rapidly and completely, including dilute thrombin time and ecarin clotting time. Not all institutions have these assays available.
            - The dose that seems to 'work' the best is 5 gm given IV (two-2.5 gm infusions given no more than 15 minutes apart).
            - Median investigator-reported time to cessation of bleeding was 11.4 hours in the NEJM study.
            - 21 of the 90 patients in the NEJM study had 'serious adverse effects' including thrombotic events.
                - 11 patients had sub-therapeutic levels of Dabigatran upon arrival that should have been excluded from the study. Including these patients could **falsely over-inflate the results** of the study.
            - The acquisition cost of this medication will most assuredly be high if and when it is FDA-approved in the U.S.
            - Another helpful reference: http://www.emdocs.net/reversal-of-anticoagulation-an-update/
        - Andexanet alfa

- Not to be outdone by the recent FDA approval of Idarucizumab to reverse dabigatran, a new factor Xa reversal agent is under investigation. "Andexanet binds and sequesters factor Xa inhibitors within the vascular space, thereby restoring the activity of endogenous factor Xa and reducing levels of anticoagulant activity, as assessed by measurement of thrombin generation and anti factor Xa activity, the latter of which is a direct measure of the anticoagulant activity." (Siegal DM, et al. N Eng J Med 2015;373:2413-24)
    - **Design** - Two parallel randomized, placebo-controlled trials (ANNEXA-A [apixaban] and ANNEXA-R [rivaroxaban]) were conducted in healthy vounteers to evaluate the ability of andexanet to reverse anticoagulation, as measured by the percent change in anti factor Xa activity after administration.
    - **What they Found** - Compared to placebo, andexanet significantly reduced anti-factor Xa activity, increased thrombin generation, and decreased unbound drug concentration in both the apixaban and rivaroxaban groups.
    - **Application to Clinical Practice**
        - This drug is not yet FDA approved.
        - These trials were funded by the maker of andexanet (Portola Pharmaceuticals) and supported by the makers of apixaban and rivaroxaban.
        - Studies are needed in patients requiring urgent reversal.
        - The trials looked only at laboratory markers of anticoagulation. We don't know how fast (or the extent of) the reversal activity is in the clinical setting.

- New antibiotic
    - Avycaz is a fixed-combination drug containing ceftazidime, a previously approved cephalosporin antibacterial drug, and avibactam, a new beta-lactamase inhibitor
    - Avycaz is the fifth approved antibacterial drug product designated as a Qualified Infectious Disease Product (QIDP). This designation is given to antibacterial products to treat serious or life-threatening infections under the Generating Antibiotic Incentives Now (GAIN) title of the FDA Safety and Innovation Act.
    - As part of its QIDP designation, Avycaz was given priority review, which provides an expedited review of the drug’s application. The QIDP designation also qualifies Avycaz for an additional five years of marketing exclusivity to be added to the five-year exclusivity period provided by the Food, Drug, and Cosmetic Act.
    - Indications
        - Adults with complicated intra-abdominal infections (cIAI), in combination with metronidazole
        - Adults with complicated urinary tract infections (cUTI), including kidney infections (pyelonephritis)

- Avycaz should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria and who have limited or no alternative treatment options
- There has already been at least one report of resistance (*Antimicrob Agents Chemother* 2015;59(10):6605-7)
- http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435629.htm

- Reversing Nondepolarizing Neuromuscular Blockers
  - After three failed attempts, the FDA finally granted approval for Merck's non-depolarizing neuromuscular blocker reversal agent sugammadex (Bridion). Though the product has been used in Europe and Asia for several years, hypersensitivity concerns led to the delayed approval in the U.S.
  - **Important points**
    - Reverses rocuronium, vecuronium, and to a lesser degree, pancuronium
    - Full reversal obtained about 3 minutes after administration
    - Eliminated entirely by the kidneys in about 8 hours (6 times longer in patients with CrCl < 30 mL/min)
    - Dosing is generally 2-4 mg/kg. Total body weight should be used in obese patients
  - **Application to Clinical Practice**
    - Potential for use in situations where a neuro exam is needed shortly after intubation (eg, status epilepticus, ICH)
    - The risk of serious hypersensitivity appears to be < 1% in published literature
    - Cost will most assuredly be high
    - Long duration in patients with reduced kidney function means further attempts to re-paralyze with roc, vec, or pancuronium may be unsuccessful
  - Additional reading
    - The EM PharmD blog discusses sugammadex's approval in more detail (http://empharmd.blogspot.com/2015/12/sugammadex-revisited.html)
    - Welliver M, et al. Worldwide experience with sugammadex sodium: implications for the United States. *AANA J* 2015;83(2):107-15. [PMID 26016169]
    - Welliver M, et al. Discovery, development, and clinical application of sugammadex sodium, a selective relaxant binding agent. *Drug Des Devel Ther* 2009;2:49-59. [PMID 19920893]
    - Staals LM, et al. Reduced clearnace of rocuronium and sugammadex in patients with severe to end-stage renal failure: a pharmacokinetic study. *Br J Anaesth* 2010;104(1):31-9. [PMID 20007792]
    - Llaurado S, et al. Sugammadex ideal body weight dose adjusted by level of neuromuscular blockade in laparoscopic bariatric surgery. *Anesthesiology* 2012;117(1):93-8. [PMID 22549697]
- Narcan (naloxone) Nasal Spray

- On November 18, 2015, the U.S. Food and Drug Administration approved Narcan nasal spray, the first FDA-approved nasal spray version of naloxone hydrochloride, a life-saving medication that can stop or reverse the effects of an opioid overdose.
- Drug overdose deaths, driven largely by prescription drug overdoses, are now the leading cause of injury death in the United States – surpassing motor vehicle crashes. In 2013, the Centers for Disease Control and Prevention reported the number of drug overdose deaths had steadily increased for more than a decade.
- Until this approval, naloxone was only approved in injectable forms, most commonly delivered by syringe or auto-injector. Many first responders and primary caregivers, however, feel a nasal spray formulation of naloxone is easier to deliver, and eliminates the risk of a contaminated needle stick. As a result, there has been widespread use of unapproved naloxone kits that combine an injectable formulation of naloxone with an atomizer that can deliver naloxone nasally. Now, people have access to an FDA-approved product for which the drug and its delivery device have met the FDA's high standards for safety, efficacy and quality.
- Narcan nasal spray does not require assembly and delivers a consistent, measured dose (4 mg) when used as directed. This prescription product can be used on adults or children.. The drug is sprayed into one nostril while the patient is lying on his or her back, and can be repeated if necessary.
- In clinical trials conducted to support the approval of Narcan nasal spray, administering the drug in one nostril delivered approximately the same levels or higher of naloxone as a single dose of an FDA-approved naloxone intramuscular injection, and achieved these levels in approximately the same time frame.
- NARCAN® (naloxone HCl) Nasal Spray 4 mg is scheduled to become commercially available early 2016.
- Group purchasers, such as law enforcement, fire-fighters, first responders, departments of health, local school districts, colleges and universities, and community-based organizations that order directly from Adapt Pharma, are eligible for a discounted **Public Interest Price** of **$37.50 per 4mg NARCAN Nasal Spray device** ($75 for a carton containing 2 devices of NARCAN Nasal Spray 4mg).
- Additional reading
  - http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473505.htm
  - http://www.narcannasalspray.com/pdf/NARCAN-Quick-Start-Guide.pdf