2.22 Pharmacy

Purpose

To provide guidelines for infection control in the Pharmacy

Audience

All UTMB employees, contract workers, volunteers, and students

Personnel

- Personnel shall comply with the Employee Health Center guidelines for their area.
- Eating and drinking shall be confined to designated areas.
- Suspected or known exposure to or acquisition of a communicable disease shall be reported immediately to the Employee Health Center or the Department of Healthcare Epidemiology.
- A clean scrub suit or lab jacket shall be worn daily when providing patient care.
- Personnel entering a patient room shall strive to keep their attire free from patient contact and soilage with the patient's blood or other body fluids or excretions.
- All personnel shall follow the instructions posted on the door or isolette of a patient in isolation. All guidelines shall be followed. The patient's chart, records, or papers which will be removed from the patient's room shall not be placed on a surface in the room.

Parenteral Fluids

- Total parenteral nutrition fluids shall be admixed (compounded) in the pharmacy. In general, parenteral fluids shall be admixed by or under the guidance of the pharmacy department.
- Personnel shall wash their hands prior to admixing parenterals. Thereafter, handwashing shall be performed prior to admixing parenterals and when personnel are returning from areas outside the admixture area. Handwashing shall be performed appropriately (see policy: 1.14 Hand Hygiene for all Healthcare Workers). Gloves and gowns shall be worn when working with chemotherapeutic agents.
- All unopened containers of parenteral fluids (bulk solutions, vials, ampules) shall be checked for evidence of contamination and deterioration. Color, clarity, and presence or absence of precipitate shall resemble the normal state. Containers shall be checked for integrity (absence of cracks and leaks) and for evidence of particulate matter. The manufacturer's expiration date shall be checked before admixing and again before the final product is dispensed. If any problem is noted, the fluid shall not be used.

- A distinctive label shall be attached to each admixed parenteral solution, stating as a minimum, the additives, their dosages, the date and time of compounding, the expiration time, and the person who did the compounding.
- Irrigation fluids such as saline for irrigation and water for irrigation shall be discarded 24 hours after opening. The recalculated expiration date and the person's initials shall be placed on the container as follows: "Exp 7/11/96 MS." The date opened shall not be placed on the vial. The initial "X" shall not be used in place of "Exp."
- The Pharmacy and Materials Management shall have access to the lot numbers of parenteral fluids shipped to the institution so that fluids can be traced if contamination at the time of manufacture or during admixture in the pharmacy is suspected.
- All admixed fluids shall be stored according to accepted guidelines noted in the Pharmacy Policy and Procedure Manual and in accordance with the manufacturer's guidelines.
- A laminar-flow hood with vertical flow shall be used for compounding hyperalimentation fluid and other parenteral fluids.
- The Pharmacy shall follow the manufacturer's instructions for use of the laminar flow hood and in addition, the following:
  - A minimum number of objects, vials and other containers shall be placed in the hood.
  - The ultra-high efficiency filter shall be tested for integrity and the stated air velocity verified at least annually and whenever the hood is moved (filter integrity can be checked with a "Dop" smoke-detection system).
- All surfaces inside the hood (excluding filter surfaces) shall be wiped clean with 70-90% ethyl or isopropyl alcohol or a disinfectant-detergent solution before each use and several times per day if the hood is in continuous use.

Single and Multidose Vials

Definition: a single dose vial is one, which is labeled as such by the manufacturer--normally the product labeling has no documentation of the presence of a preservative. Single dose (single use) containers shall be used for admixture when possible. Vials are preferred to ampules. Single dose vials used in the pharmacy under aseptic conditions in a laminar flow hood may be used until the end of the shift. Opened single dose vials shall be stored for the duration of the shift

under the same conditions as the unopened vial (e.g., if the unopened vial requires refrigeration, the opened vial shall be refrigerated). Single dose vials shall be discarded at the end of each shift regardless of when opened during the shift.

Ampules and the remaining product shall be discarded after single use. The container shall not be used as a reservoir for multiple doses unless the doses are drawn in an uninterrupted fashion.

Use the following guidelines to determine the shelf life of a multiple dose vial:

Multidose vials must be discarded when empty, when suspected or visible contamination occurs, when deterioration is suspected, or when particulate matter is present.

AND

Once opened, multidose vials must be given an expiration date of 28 days or the manufacturer’s expiration date, whichever is less.

For powders that are reconstituted, an expiration date is calculated based on the manufacturer's recommendation stated on the vial or in the insert or 28 days, whichever is less.

When vials have been reconstituted, the expiration date and the person's initials shall be placed on the vial as follows: "Exp mm/dd/yy MS". The date opened shall not be placed on the vial. The initial "X" shall not be used in place of "Exp".

AND

Multidose vials must be discarded when they have been stored improperly.

NOTE: The assigned expiration date of multidose vials may be shorter than that of the manufacturer. However, under no circumstance will an assigned expiration date exceed the manufacturer's expiration date.

General Guidelines

- Dispensing counters used in conjunction with admixing parenterals shall be cleaned with a disinfectant solution at the beginning of each shift and more often if necessary.
- Tablet and capsule counting equipment shall be clean at all times.
- Aseptic techniques for IV admixing shall be followed.
- Sterile supplies shall be transported in such a way as to prevent contamination, such as puncturing a container or alteration of a wrapper.
- The Pharmacy shall clearly label germicides, disinfectants, etc., with warnings regarding shelf-life, safety, and other information as necessary.
- All drugs shall be stored in clean, dust-free areas. Bulk drug packages shall not be placed directly onto the floor, but elevated on shelves or pallets at least 8 inches off the floor.

Guidelines for Use of Specific Drugs

- Botulinum toxin A (Botox) (See attached Appendix)
    - Reconstitute Botox with preserved or nonpreserved saline if the whole vial will be used in one clinic session.
    - Reconstitute Botox only with preserved saline when it is likely that the whole vial of Botox solution will not be used in a clinic session. The remaining contents of the vial may then be stored up to 14 days when refrigerated at 4°C.

Appendix

Use of Botulinum Toxin A (Botox)

Investigation

Sources of Information

1. Review of documents prepared by the UTMB Department of Pharmacy
    a. Extensive review of the product including a description of the medication, its clinical pharmacology, clinical use, indications and contraindications for use, precautions, drug interactions, adverse reactions and dosage and administration.
    b. Extensive critical analysis of eight publications on Botox.
    c. A table of information gathered from other institutions where Botox is used.
2. Extensive computer-based literature search and review of references in articles downloaded.
3. Worked with 2 research librarians searching for publications on contamination of reconstituted Botulinum toxin A and for any infections complications of Botox injections in patients over the last 15-20 years.
4. Interviewed 2 Healthcare Epidemiologists at University Medical Centers.

Results

1. There are 3 publications on contamination of Botox after reconstitution with diluents.
    a. Anderson ER Jr. Proper dose, preparation, and storage of Botulinum neurotoxin serotype A. Am J Health-Syst Pharm 2004;61(Suppl 6):S24-S26.
    b. Alam M, Yoo SS, Wrone DA, et al. Sterility assessment of multiple use Botulinum A exotoxins vials: a prospective simulation. J Am Acad Dermatol 2006; 55:272-275.
    c. Menon J, Murray A. Microbial growth in vials of Botulinum toxin following use in clinic. Eye 2007; 21:995-997.

    The first publication discusses the proper reconstitution and use of Botulinum toxin A but provides no data on contamination of Botox vials or post injection infections. The second reference found no growth in 11 vials of Botox after use at room temperature for 4 hours. The third publication described culture of 127 vials used up to 7 weeks after reconstitution. Vials were cultured by adding thioglycolate broth. All were culture negative. The problem with interpretation of this study's results was that all vials were reconstituted with saline with preservative.

Conclusions: No evidence that Botox vials become contaminated after prolonged use, but weak study design and small numbers in these investigations fail to establish that prolonged usage is safe and without risk of contamination.

2. There are six studies on the effect of prolonged storage (refrigerated or fozen) of Botox on clinical efficacy.
    a. Sloop RR, Cole BA, Escutin RO. Reconstituted Botulinum toxin type A does not lose potency in humans if it is refrozen or refrigerated for 2 weeks before use. Neurology 1997; 48:249-253.
    b. Hexsel DM, DeAlmeida AT, Rutowitsch M, et al. Multicenter, double-blind study of the efficacy of injections with Botulinum toxin type A reconstituted up to six consecutive weeks before application. Dermatol Surg 2003; 29:523-529.
    c. Thomas JP, Siupsinskiene N. Frozen versus fresh reconstituted Botox for laryngeal dystonia. Otolaryngol Head Neck Surg 2006; 135:204-208.
    d. Parsa AA, Lye KD, Parsa FD. Reconstituted Botulinum type A neurotoxin: clinical efficacy after long-term freezing before use. Aesth Plast Surg 2007; 31:188-191.
    e. Yang GC, Chiu RJ, Gillman GS. Questioning the need to use Botox within 4 hours of reconstitution. A study of fresh vs 2-week-old Botox. Arch Facial Plast Surg 2008; 10:273-279.
    f. Paik N-J, Seo K, Eun HC. Reduced potency after refrigerated storage of Botulinum toxin A: Human extensor digitorum brexis muscle study. Mov Disord 2006; 21;1759-1762.

Five of the six studies found that storage of Botox under different conditions and for varying lengths of time did not reduce the potency of the product. Only one of the studies was a prospective controlled trial. One trial was a prospective blinded trial where fresh Botox was injected into muscles on one side of the face and stored Botox was injected into muscles on the opposite side. There were 40 patients in the study. The number of subjects in each study ranged from 8 to 88 with a mean of 48.5 subjects and a median of 41.5. Outcomes of Botox injection were assessed in 2 studies with electromyograms, in 2 studies with photographs and in the remaining two by post injection telephone interviews of patients. Subjects served as their own controls in all but one study. Statistical analyses were done in 5 of 6 studies.

Conclusions: It is difficult to draw definitive conclusions from these small suboptimally designed studies. However, 5 of 6 of the studies observed no change in efficacy after storage of Botox in the refrigerated or frozen state, no infectious complications were observed in any of the 291 subjects in these investigations and in 2 of the studies, measurement of responses by electromyography showed no difference in response between freshly prepared and stored Botox.

3. There are two studies on use of Botox reconstituted with preserved saline.
    a. Alam M, Dover JS, Arndt KA. Pain associated with injection of Botulinum A exotoxins reconstituted using isotonic sodium chloride with and without preservative. A double-blind randomized controlled trial. Arch Dermatol 2002; 138:510-514.
    b. Kwiat DM, Bersani TA, Bersani A. Increased patient comfort utilizing Botulinum toxin A reconstituted with preserved versus non-preserved saline. Opthal Plast Reconstr Surg 2004; 20:186-1789.

In these two studies there were 20 patients studied retrospectively and 35 studied prospectively. Both of the prospectively conducted studies were stated to be randomized controlled trials, but one study was not randomized and in the other study it was not possible to discern whether or not it was randomized. Both studies were controlled by injection of nonpreservative saline reconstituted Botox on one side of the face and Botox reconstituted with preserved saline on the other side of the face. Assessment of patients included differences in pain on injection of the two preparations on opposite sides of the face at time of injection and follow up. Differences in the long-term efficacy of injection with the two preparations of Botox were assessed by self-reports from patients and follow-up visits in the clinic with treating physicians within 4 months of the treatments.

Thirty-four of the 35 (97%) prospectively studied patients in these two studies combined noted less pain on the side of the face injected with the preserved saline reconstituted Botox. In neither study did self-reports from patients or observations of physicians note any difference in efficacy between he two sides of the face injected with either preserved or nonpreserved saline reconstituted Botox.

Consensus recommendations have been published in which a panel of ophthalmologists and dermatologists have made recommendations for the use of Botox. They indicate that preserved saline is preferred for reconstitution of Botox.

Carruthers, J, Fagien S, Matarasso SL. Consensus recommendations on the use of Botulinum toxin A in facial aesthetics. Plast Reconstr Surg 2004; 114(Suppl 6):15S-22S.

Conclusions: Two studies with limited numbers of prospectively studied patients observed that injection of Botox reconstituted with preserved saline caused significantly less pain on injection without apparent loss of efficacy. A consensus publication on use of Botox indicated that preserved saline was preferred for reconstitution of Botox.

4. Review of the literature for published reports of infectious complications of Botox injections. Search conducted by research librarian for a period extending back 15-20 years.

   Conclusions: No published reports on infectious complications of Botox injection.

5. Interviews of Healthcare Epidemiologists at other university medical centers.
   a. At Northwestern University, Botox is reconstituted with saline and used within 4 hours.
   b. At the University of North Carolina, when multiple use is necessary, Botox can be used for 7 days when reconstituted with saline and for 30 days when reconstituted with benzyl alcohol containing saline.

6. Recommendations
   a. Reconstitute Botox with preserved or nonpreserved saline if the whole vial will be used in one clinic session.
   b. Reconstitute Botox only with preserved saline when it is likely that the whole vial of Botox solution will not be used in a clinic session. The remaining contents of the vial may then be stored up to 14 days when refrigerated at 4°C.