The Lost Art of Compounding
June 18, 2010

Goal

- Present a description of compounding pharmacy
- Demonstrate where compounding can provide solutions to patient problems

Pre Lecture “i-Clicker” Test

- Which agency is more restrictive in the manufacturing and compounding of drugs by a pharmacy?
  
  A. Texas State Board of Pharmacy.
  B. FDA.
  C. Both equally.
Pre Lecture “i-Clicker” Test

• Is the art of compounding is still taught in Pharmacy School?
  – A. True.
  – B. False.

Pre Lecture “i-Clicker” Test

• Compounded drugs do not have to be tested for quality nor stability?
  A. True.
  B. False.

Objectives

• Discuss the role of compounding pharmacist and practitioner within the triad relationship for meeting individual patient needs
• Discuss the training, equipment, specialty dosage forms, and quality control required for contemporary compounding
• Discuss general areas of possible need in which the compounding pharmacist can help solve problems
• Discuss specific disease states or disorders to which the compounding pharmacist can apply his unique training, equipment and knowledge.
Pharmacy

- The **art** or profession of preparing and preserving drugs, and of **compounding** and dispensing medication **according to the prescriptions** of physicians.

-----Early 20th century Webster Dictionary

History of Compounding

- Bagdad, 9th century first recorded pharmacy.
- 1800’s all drugs were compounded.
- Industrial revolution brought out the beginning of manufactured drugs.
- 1940, more than 50% of drugs were compounded.
- 1965, less than 10% of drugs were compounded.
- 2010, 5% of drugs are compounded today.

What is Compounding?

- Compounding is the traditional method of preparing **customized medications** from scratch to help meet unique physician and patient needs.
Compounding

• Focuses on providing innovative medications through the use of unique dosage forms, alternative therapies, and specialized education and equipment.
• The ultimate goal in compounding is to help the patient achieve a positive therapeutic outcome.

Compounding vs. Manufacturing

• Manufacturing
  – No specific patient in mind when drug is produced
  – Has prescribers matching patients to the product available
  – Economic considerations limit choices in drug dosages and dosage forms
• Compounding
  – Making the formula match the individual patient’s needs
  – Administer the drug to the site of action in the most effective dosage form available

The Triad

A Healthy Relationship is the “KEY” to compounding
Improve Therapeutic Outcomes.....

......by solving the problem:

• Avoidance of dyes, preservatives, fillers, actives
• Palatable liquid medications
• Administrable dosage form
• Dose, dosage form, or medication not commercially available
• Combination or sustained release therapy to improve compliance
• Cost effective therapy

Requirements for a Compounder

• Specialty Training
  – Equipment, procedures, dosage forms, etc.
• Quality Control
  – Policy & Procedures
  – Testing of personnel and products

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Quality Assurance and Quality Control of Compounded Preparations

Compounding Guidelines

• NABP: Good Compounding Practice Guidelines
• United States Pharmacopeia (USP): Chapters on Pharmaceutical compounding, non-sterile and sterile as well as good compounding practices
• USP 795 for non sterile preparations
• USP 797 for sterile preparations

Contemporary Compounding Equipment and Devices

“To provide patients with a customized dosage form, using the best technology and equipment available, in an efficient and cost effective manner”
Electronic Balance

Electronic Balance is used to measure mass to a very high degree of precision and accuracy. Calibrated daily. Inspected annually by the State board.

Powder Hood

The Powder Hood provides a safe environment for technicians to crush tablets, fill capsules, and handle drugs.

Electronic Mortar & Pestle

The “EMP” provides pharmacists with the modern way to compound ointments, creams, gels and suspensions.
Ointment Mill
The ointment mill mixes powders, crystals and creams into a smooth, finished product with reduced particle size.

Homogenizer
A homogenizer is a high-speed blender distinctly suited to reduction of particle size for suspensions and lotions. It makes great smoothies too!

Capsule Machine
Able to quickly compound in 100 count and 300 count lots. Average time to fill one lot is 5 minutes.
Unique Dosage Forms

Compounded Dosage Forms

- Oral capsules and liquids
- Suppositories and enemas
- Otic preparations
- Topical creams, lotions, ointments, gels, powders, and sprays
- Oral adhesives, mouthwashes and rinses
- Sterile products:
  - Inhalation solutions, Injections, Ophthalmics, Nasal, and TPNs

Capsules

- Combinations
- Different strengths match individual's needs
- Commercial product no longer available
- Avoid excipients patient may be sensitive to
- Immediate release, sustained release and enteric-coated formulations
Natural Colorants

- Natural powders that impart dye free color
  - Coenzyme q 10—orange
  - Vitamin B12—red, pink
  - Riboflavin or beta carotene—yellow
  - Green tea extract—green
  - Charcoal—grey
  - Ginger root—brown

Compounded Oral Liquids

- Difficulty swallowing
  - Medication not available as liquid
- Avoid unwanted ingredients
  - Free of dyes, sugar, alcohol and preservatives
- Increased compliance
  - Much more palatable preparations with choice of multiple sweeteners and flavors
- Anhydrous formulations
  - May be used if aqueous stability a concern

Customized Flavors for People and Pets

Compounding pharmacists can offer more than 100 flavors to satisfy our patients, both human and pet.
Suppositories and Enemas

- Rectal or vaginal use
- Difficulty in swallowing
- Nausea/vomiting occurring
- Injections cause pain, anxiety
- Rapid local affect
  - Hemorrhoids
  - Irritable Bowel Syndrome
  - Crohn’s disease
  - Anesthetic, anti-inflammatory, steroid agents
- Good absorption route for many drugs
  - Prevents 2/3 of first pass effect

Compounded Sterile Products

- Injections—aqueous and oil vehicles
- Ophthalmic and Nasal solutions, suspensions, sprays, and ointments
- TPNs and IV admixtures
- Inhalation solutions
- Irrigating solutions

Transdermal Gels

- A specially prepared emulsion that penetrates the skin and gets medications into the bloodstream quickly
- Effective dosage form for the patient who can’t swallow
  - May be used for systemic or local effects
Medicated Lollipops

- Local effects
- Systemic effects
- Combination effects

Medicated Lollipops

- Nicotine 2mg and 4 mg
- Diethylpropion HCL 25mg (and chromium)
- Electrolytes or pilocarpine for dry mouth
- Menthol & eucalyptus for cough and sore throat
- Midazolam prior to dental procedure
- Tetracaine 0.5% pre-exam or post-surgery
- Amphotericin or clotrimazole for fungal infections
- Healing & numbing agents to treat mouth lesions
- Fentanyl in sorbitol base.

Tablet Triturates

Animal Treats
Tablet Triturates

- Rapid onset
  - Migraine headache
  - Emesis (canine use)
  - Erectile dysfunction
- Sublingual / Buccal absorption
  - No first pass effect
  - No stomach acid degradation
- Cost effective
- Convenient

Mini Troches

- Administration
  - Buccal or S/L
  - Vaginal
  - Uses
    - Hormone
    - Nicotine
    - Vet

Rapid Dissolve Tablets
Rapid Dissolve Tablets

- Drugs being used:
  - Hormones
  - Sildenafil
  - Piroxicam
  - Narcotics
  - Naloxone
  - Methylphenidate
  - Promethazine
  - Prednisolone

RDT’s are gluten free and dye free orally dissolved tablets for medications to be absorbed buccally or sublingually.

The Polyox Bandage

- Designed for oral use
- Superior oral bandage
  - Stays in place for hours even if “rubbed”
- Used for any appropriate drug therapy desired
  - Antihistamine, anesthetic, antiviral, antifungal, anti-inflammatory, etc., or combinations

The Rectal Rocket

- Designed to get the drug(s) to the site of action
- Combine anesthetic and anti-inflammatory drugs
- Also used for healing fissures
What needs to be sterile?
USP Chapter <797>

- Baths and soaks for live organs and tissues
- Implants
- Injections
- Powders for injection
- Irrigations
- Inhalations
- Ophthalmics
- Nasal preparations

Compounding for Pain Management

- Individualized dosing
- Combination products
- Choice of multiple dosage routes
- Utilization of action on central and/or peripheral receptors
- Adjustment of transdermal penetration rate and depth to reach and depot at receptor
- Able to affect nociceptive, NMDA and AMPA receptors; trigger points, and transmission points

Neuropathic Pain Treatment

- Block the physiologic nerve pathways
  - NMDA antagonist
  - Calcium Channel
  - AMPA antagonist
  - MU receptor
  - Magnesium Channel
  - GABA agonist
Transdermals for Neuropathies

- NMDA-Ca++ channel blockers:
  - Ketamine, Orphenadrine, Amantadine, DM, Magnesium, Haloperidol, Nylidrin
- AMPA-Na+ channel blockers:
  - Gabapentin, Carbamazepine, Lidocaine, Mexilitine, Valproic Acid, Phenytoin
- Glutamate antagonist: Gabapentin
- Alpha-2 agonist: Clonidine

Transdermals for Neuropathies

- GABA-b agonists: Baclofen (Klonopin is non-specific gaba agonist)
- Substance P inhibitors: Capsaicin, Morphine Sulfate, Loperamide
- NE modulators: Tricyclic antidepressants (Amitriptylene, Desipramine), Guanethidine
- Alpha-1 antagonists: Prazosin, Phentolamine
- Non-NMDA Ca++ Channel blocker: Nifedipine

Diabetic Neuropathy

- Agents to treat pain
  - Neuropathic agents
    - Transdermal application
      - Avoid systemic side effects
      - Efficient deliver of drug(s) to site of application
      - May administer multiple drugs in one dosage form
Circulation Problems

• Nifedipine
  – Calcium channel blocker
  – 80 mg (1/2 ml) of 16% PLO bid for “black toe”
  – 0.5% to 2.0% for larger areas, less severe loss of circulation
  – Increase blood flow/nutrient supply to wounds


• Pentoxifylline
  – Affects platelet flexibility and blood flow
  – Anti-inflammatory
    • Inhibits Tumor Necrosis Factor Apha (TNFα)

  Infect Immun 1988;5:1772-1729

Exercise and Sports Injuries

• Analgesic rubs and sprays
  – “Caine” anesthetics, salicylates, capsaicin,
  – Anhydrous trigger point gels
    • NSAID and gabapentin or diphenhydramine

• LAT gel or spray
  – Floor or “carpet” burns, “strawberries”, bloody noses, and bleeding cuts
  – Stop bleeding and pain of lacerations
  – Spray or apply directly to area or to gauze; hold on area for 15-30 seconds
  – Lidocaine, tetracaine, epinephrine

Triple Anesthetic ointment (BLT)

• Benzocaine 20%, lidocaine 6% and tetracaine 4% (BLT) compounded vs. EMLA®, ELA-MAX 5® and Topicaine®
  – At 15, 30, 45 and 60 minute pain scores were significantly lower with BLT
  – Compounded gel provided superior local anesthesia
Exercise and Sports Injuries

- Transdermal gels
  - Inflammation and pain
    - NSAIDs: ketoprofen, ibuprofen, Diclofenac, etc.
    - Dexamethasone
    - Combinations
      - Combine NSAIDs to increase duration
      - Combine with muscle relaxants, neuropathic agents, etc.

Exercise and Sports Injuries

- Transdermal gels
  - Muscle relaxants
    - Sprains, cramps, muscle aches
      - Guaifenesin, cyclobenzaprine, magnesium
  - Dextromethorphan
  - Neuropathic agents
    - Ketamine, gabapentin, clonidine, amitriptyline, baclofen, etc.

KETA-LIDO-PRIL0 in PLO

- Ketamine 10%........NMDA blocker
- Lidocaine 5%.........Local anesthetic
- Prilocaine 5%.........Local anesthetic
- DMSO 5%
- Apply 1-2gm 3-4 x daily
- Great for burning nerve pain. PLO gel drives the drugs into the skin starts to give relief in 2-3 minutes, lasts 3-6 hours.
10-2-2-10 Pain Gel

- KETOCAM-CYCLO-KETA in PLO (10-2-2-10)
  - Ketoprofen 10% ..........Anti inflammatory
  - Piroxicam 2%.............Anti inflammatory
  - Cyclobenzaprine 2%......Muscle relaxant
  - Ketamine 10% ............NMDA blocker
  - DMSO 5%

  - Apply 1-2 gm 3-4 x daily Great for acute and chronic tissue and bone pain. PLO gel drives the drugs into the skin, starts to give relief in 2-3 minutes, lasts 3-6 hours.

PainFree-IBU Fast Gel

- Ketamine 10%............NMDA Blocker, Analgesic
- Gabapentin 4%............Nerve Blocker
- Ibuprofen 10%............Anti inflammatory
- Diclofenac 4%............Anti inflammatory
- Amitriptyline 1%.........Nerve Blocker
- Cyclobenzaprine 2%......Muscle Relaxant

  - Apply 0.5-1.0ml 3-4 x daily
  - Use 1-4 drops on the affected area either alone or after the PLO gels. Response is in 1-2 minutes.

Phonophoresis (Ultrasound) Gels

- Hydroxyethylcellulose gels
- Anti-inflammatory:
  - Betamethasone 0.05%
  - Fluocinonide 0.05%
  - Hydrocortisone 1% - 10%
  - Ketoprofen 5% - 10%
Iontophoresis Solutions

- Anti-inflammatory
  - Hydrocortisone
  - Dexamethasone 0.2% - 0.4%
  - With or without lidocaine 4%
  - NSAID's

Compounded Hospice Solutions

- End of Days care (ABH Topical Gels)
- Pain management
- Nausea & vomiting
- Wound care
- Ulcer prevention
- Mouth ulcers
- Saliva stimulants
- Itching
- Constipation, dehydration, and diarrhea

Wound Therapy Options

- Healing agent
  - Misoprostol 0.0024%
  - Phenytoin 5%
  - +/- Testosterone 0.5%
  - Keto-Lido 2%
  - Aloe Vera 0.2%
  - Applied bid x 6 months
- Nifedipine and/or Pentoxifylline transdermally to increase circulation.
- Metronidazole, gentamycin, Vancomycin if infection present.
Malodorous Wounds

- Malignant cutaneous wounds, ulcerated tumors, fungating tumors, benign cutaneous ulcers
- Metronidazole
  - Effective against anaerobic bacteria that cause these foul and distressing odors
  - Alternatives: gentamycin and chloromycetin

Doxepin Oral Rinse

- Oral mucosal pain due to cancer or cancer therapy
- 41 patients rinsed with a single dose of a doxepin 0.5% solution
- More than 50% reduction of pain intensity
- Pain relief for >3 hr, return to baseline in 4 hr
  - Extended duration due to analgesic effect
- Well tolerated
  - Infrequent mild stinging
  - Some mild sedation
Compounding for Pediatrics

- Flavoring and sweetening for compliance
- Autism - Down’s Syndrome - ADD
- Diaper rash - Colic
- Cradle Cap
- GERD
- Topical anesthesia
- Laxatives
- Nausea & vomiting
- Chicken Pox
- Antibiotic compliance
- Pediatric dermatology: rash, atopic dermatitis, eczema, etc.

Flavoring

- For infants, keep the flavoring sweet and simple
  - Marshmallow
  - Vanilla

A Bit too much Stevia!
Dermatology Compounding

- Psoriasis, Eczema, Atopic Dermatitis
- Rashes, itching
- Fungal, viral and bacterial skin infections
- Fungal nail infections
- Warts
- Hyperhidrosis
- Wrinkles, age spots, vitiligo
- Acne Vulgaris and rosacea
- Burns, scars, wound healing
- Specific disease states (Ichthyosis, Molluscum Contagiosum)
- Head and body lice, parasites

Acne Vulgaris

- Niacinamide 4% Gel provides potent anti-inflammatory activity
  - Equal in efficacy to 1% Clindamycin
- Azelaic acid 2%
- Spironolactone 5%
- Sulfur 2-4%
- Lipoic acid 0.5%
- Isotretinoin topical 0.05%

Rosacea

- Common inflammatory disease generally confined to the face, principally the cheeks, forehead, nose, and chin

  Treatment options

- Topical metronidazole – considered first line of therapy
- Azelaic acid 15-20% cream or gel
- Erythromycin 2% solution
- Topical clindamycin
- Oral or topical isotretinoin
BHRT Compounding

On January 9, 2008, FDA took action on behalf of pharmaceutical manufacturer Wyeth to impose harmful restrictions on the compounding and dispensing of bio-identical hormone replacement therapy (BHRT), specifically compounded medicines containing the drug estriol. This action has critical implications for pharmacists, patients and physicians.

Visit my website to view a slide presentation on the basics of Bio-identical Hormone Restoration Therapy and sign up to protect your right to compound and have access to BHRT.

Compounding for the Ob-Gyn

- Nausea & vomiting
- Liquid vitamin/mineral combinations
- Hemorrhoids
- Backache
- Augmenting lactation
- Initiation of milk let-down
- Vulvodynia
- Bio-identical hormone therapy
Augmenting Lactation

- **Domperidone**
  - Peripheral dopamine antagonist
  - Does not cross the blood-brain barrier
  - Small amount secreted in breast milk due to high protein binding
  - Dose: 10 mg three times daily to 20 mg four times daily
  - Usually taken for 3-8 weeks but adoptive mothers often take for longer periods
  - Effect seen within 3 to 4 days with maximum effect in 2 to 3 weeks

Oxytocin

- Indicated for initial milk let-down
- Administered as 40 units/ml nasal spray
- 1 spray in one or both nostrils 2 to 3 minutes prior to nursing or pumping milk from breasts
- Recommended to only use for a couple of days so that the body is able to develop an independent let-down

Topical Treatments of Vulvodynia

- Amitriptyline 2% / Baclofen 2%
- Atropine 0.54%
- Gabapentin 6-10%
- Ketamine 10-20%
- Lidocaine 2-5%
- Doxepin 5%
- All in oil-in-water emulsion cream bases
- No ETOH in base.
Morning Sickness

• Menadione and Ascorbic acid
• Theory is to reduce placental capillary permeability and prevent transfer of the “vomiting factor” to the expectant mother
• 70 women given 25 mg ascorbic acid and 5 mg menadione bisulfite
• 64 patients had complete remission of symptoms within 72 hours

Aug 1952; Am J Obst & Gynec p 416-418

Anal Fissures and Spasms

• 30-40% of population suffers from proctologic pathologies once in lifetime
• Glyceryl Trinitrate (Nitroglycerin)
  – 0.2% ointment bid w/ lido 4% x 8 wks, 68% healed
• Nifedipine 0.2% w/ Lido 4%
  – 20 mg p.o. bid x 8 wks, 9 of 15 healed,
  – vs 0.2% topical gel: q 12 hrs x 21 days, 95% total remission
• Diltiazem 3% and Bethanecol 0.1%
### Raynaud’s Syndrome

- Calcium channel blockers
  - Nifedipine PO 10-20 mg tid
  - Side effects in 1/3 (headache, flushing, dizziness, reflex tachycardia, peripheral edema)
  - Transdermals (0.5 to 2%)
- Pentoxifylline 5 to 15%
- Nitric oxide producing gel
  - Combine ascorbic acid and sodium nitrate gels on arm

### Promethazine Gel

- Treatment for Nausea and Vomiting for all ages. Decreased pediatric cautions.
- Topical Promethazine 12.5mg/0.1ml gel
- Apply 0.1ml to 0.2ml to the clavicular area.
- Use gloves or the patient’s finger.
- Relief in 1 min, may repeat prn,
- Better dose control, rapid response.
- Dispense 1 topical syringe for 5-10 doses.

### Burning Mouth Syndrome

- Clonazepam 0.5 or 1.0 mg troche
- Doxepin 0.5% troche or solution
- α-Lipoic acid
- Amitriptylene or Carbamazepine
- BMS formula containing salicylic acid and ethanol
  - Add 0.2% Deoxy-D-Glucose and 1% Beta glucan

*American Family Physician Feb 2002;65(4):615-620*
Rosacea
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• Topical metronidazole 4% – considered first line of therapy
• Azelaic acid 15-20% cream or gel
• Erythromycin 2% solution
• Topical clindamycin
• Oral or topical isotretinoin

Rosacea Treatment Options
• Topical sulfur 10% cream
• Topical ketoconazole 2% cream
• Oral or topical spironolactone
• Pentoxifylline
• Niacinamide 4%
• Tranilast
• Cholesteramine
• Omega 3 Fatty Acids 2.5gm daily
• Use of sunscreens
• Hormonal influence?

Podiatry Needs
• Onychomycosis
• Fungal infections
• Nail removal
• Warts
• Heel spurs
• Hyperhidrosis
• Foot odor
• Topical anesthetics
• Muscle and joint pain
• Inflammatory conditions
• Diabetic neuropathy
• Circulation problems
• Decubitus ulcers and wounds
Onychomycosis

- Topical anti-fungals
  - Wide choice of agents available
    - Fluconazole, itraconazole, ketoconazole, undecylenic acid, tea tree oil, etc.
  - Ibuprofen
    - Synergistic action with “azole” anti-fungals
  - Ease of use
    - Brush onto nail and surrounding skin with applicator twice a day

Non-surgical Nail removal

- Urea 40% ointment
  - Apply to nail at bedtime and occlude
  - Nail usually comes off within a week

Topical Cyclosporin for Psoriatic Nails

- Cyclosporin (100mg/ml) in maize oil 70:30
  - (Final conc. of 7% cyclosporin in oil)
  - Applied to nails daily for 12 weeks
  - 8 patients: complete resolution in 3 pts, substantial improvement in 5 pts

*Dermatol 2003;206(2):153-6.*
Agents Used to Treat Warts

- 2-Deoxy-D-Glucose
- Cimetidine
- Cantharidin
- Trichloroacetic Acid
- 5-Fluorouracil
- Podophyllin
- Squaric Acid, DNBC, DPCP
- Salicylic Acid up to 80%

Special Extemporaneous Formulations

- Methylphenidate: liquid, SR capsules
- Clonidine: transdermal, SR capsules
- Strattera®: anhydrous liquid and transdermal
- Caffeine: alternative strengths
- Tamiflu® suspension

Inhalation Therapies

- N-acetylcysteine (NAC) for cystic fibrosis
  - 2 to 5 ml of 20% solution tid
- Lidocaine for severe asthma or cough
  - Adults: 40-60 mg qid
  - Children: 0.8 to 2.5 mg/kg tid to qid
- Magnesium Sulfate for Asthma, emphysema, COPD (3 ml of 3.2% solution)
  - Similar results in asthma to albuterol
- Glutathione for CF, Emphysema, Asthma, and COPD (2ml, 60mg/ml qd)
Compounding is Essential to Veterinary Medicine

Meeting the unique needs of the veterinary patient……

- Lack of approved veterinary drugs
- Lack of proper strength and dosage form for animal being treated
  - Veterinary medications species specific in strength and dosage form
  - Human drugs commonly used in animals

Thank You!
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Post Lecture “i-Clicker” Test
What are the USP 795 rules?

A. United States Packaging rules for shipping drugs in the mail.
B. Quality assurance rules in non sterile compounding.
C. 795 rules of good manufacturing practices.
D. Manufacturing, packaging rules for non sterile compounding.
E. B & D
F. C & D

2. USP 797 rules for sterile packaging require the following preparations be prepared in a sterile environment and packaged as such:
A. Injectable drugs
B. Nasal preparations
C. Inhalation solutions
D. Ophthalmic preparations
E. All of the above.
F. All but Nasal.
3. Topical promethazine gel will relieve nausea and vomiting faster and more elegantly than a tablet or suppository?

   A. True
   B. False