HST-151

Drug Development

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This lecture will discuss the evaluation of new drugs (Ch. 5 of Katzung) - with the definition of drug writ large - using the field of prolonged duration local anesthesia as an example. The talk will attempt to highlight the importance of basic pharmacological concepts in drug development, but also introduce (or perhaps re-introduce) more advanced biotechnological approaches. We will not focus on the clinical or business aspects of drug development.

Outline of the Lecture

1. The Need
    - Magnitude and severity of the problem
    - What medical researchers look for vs. what the corporate world looks for
    - Existing technologies and their limitations
2. Characteristics of the hypothetical ideal solution
    - The importance of asking the right question (most importantly, perhaps: assuming we can achieve what we set out to achieve, is it actually good for our patients?)
    - The difficulty of overcoming preconceived notions
3. Ways of achieving (2)
    - New drugs and drug combinations, or new ways of using old drugs
    - New targets
    - Chemical modification of drugs
    - Novel carrier fluids
    - Microparticles
        - liposomes and similar particles
        - microspheres
4. Key concepts and how they relate (e.g. in choosing a drug or delivery system)
    - Potency, and whether it matters

- Efficacy
- Toxicity
    local: cytotoxicity, biocompatibility.
    systemic: EC50, LD50, therapeutic index
- Pharmacokinetics, phamacodynamics
- High-throughput vs. low-throughput (or, not everything can be modeled)

5. Specific examples will focus on the development of prolonged duration local anesthetics, particularly recent research by the lecturer.

Glucocorticoids prolong rat sciatic nerve blockade in vivo from bupivacaine microspheres.

Anesthesiology. 1996 Nov; 85(5): 1157-66.

BACKGROUND: Previous work showed that incorporation of dexamethasone (0.05 weight/weight percentage) into bupivacaine microspheres prolonged blockade by eight to 13 times compared with that produced by bupivacaine microspheres alone. The determinants of dexamethasone's block-prolonging effect were examined and reported here. METHODS: Polylactic-co-glycolic acid polymer microspheres (65/35) with 75 weight/weight percentage bupivacaine were prepared. Microspheres were injected adjacent to the rat sciatic nerve, and sensory and motor blockade were assessed. A procedure was developed to test drugs for block-prolonging ability in vivo by placing test drugs in the injection fluid along with a suspension of bupivacaine microspheres. RESULTS: Dexamethasone alone in suspension did not produce blockade, nor did it prolong blockade induced by aqueous bupivacaine. Bupivacaine microspheres (150 mg drug/kg rat weight) produced blockade for 6 to 10 h. Dexamethasone in the suspending solution of microspheres prolonged block by up to five times. Glucocorticoids prolonged block in proportion to glucocorticoid/antiinflammatory potency. The corticosteroid antagonist cortexolone inhibited dexamethasone's blockade-prolonging action. Durations of blockade with or without dexamethasone were unaltered by hydroxyurea-induced neutrophil depletion. Microspheres were extracted from rats at time points ranging from 7 h to 7 days, and residual microsphere dry weight and bupivacaine content were similar in groups of rats injected with either bupivacaine microspheres or bupivacaine microspheres

containing dexamethasone, respectively. CONCLUSIONS: Glucocorticoids prolong blockade from bupivacaine microspheres. The mechanism appears unrelated to the kinetics of bupivacaine release in vivo.

A re-examination of tetrodotoxin for prolonged duration local anesthesia. Anesthesiology. 1998 Jul; 89(1): 119-31.

BACKGROUND: Highly potent toxins such as tetrodotoxin that block sodium channels with great specificity have been studied for many years and can provide prolonged blockade when coadministered with vasoconstrictors or conventional local anesthetics. Their utility has been constrained, however, by systemic toxicity. The authors examined the efficacy of tetrodotoxin with and without epinephrine or bupivacaine for producing prolonged-duration sciatic nerve blockade in the rat, and they assessed the degree of concomitant toxicity. METHODS: Rats received percutaneous sciatic nerve blockade using tetrodotoxin with and without epinephrine or bupivacaine. A subset received subcutaneous injections at the nuchal midline. Nociceptive, proprioceptive, and motor blockade were quantified using contralateral leg responses as controls for systemic effects. RESULTS: Tetrodotoxin without epinephrine produced sciatic nerve blockade, but with considerable toxicity at most effective doses. Epinephrine reduced the median effective concentration of tetrodotoxin for nociception from 37.6 to 11.5 microM and prolonged its duration, such that reversible blocks lasting > 13 h were achieved. Epinephrine reduced measures of systemic distribution and increased the median lethal dose of tetrodotoxin from 40 to 53.6 nmole/kg, thus more than quadrupling the therapeutic index. Bupivacaine increased the local anesthetic potency of tetrodotoxin, reduced its systemic toxicity, and, when

coinjected subcutaneously, increased the median lethal dose from 43.7 to 47.7 nmole/kg. The addition of epinephrine did not further improve the effectiveness of the bupivacaine-tetrodotoxin combination. CONCLUSION: Combinations of epinephrine or bupivacaine with tetrodotoxin or with other high-potency toxins active on sodium channels should be examined for the potential to provide clinically useful, prolonged nerve blockade.

Biocompatibility of lipid-protein-sugar particles containing bupivacaine in the epineurium.

J Biomed Mater Res. 2002 Mar 5; 59(3): 450-9.

Novel lipid-protein-sugar particles (LPSPs) are potentially biocompatible because they are composed of naturally occurring ingredients and their expected tissue dwell times are relatively short. Here we use histological sections to study tissue reaction to LPSPs (4.4 μm median diameter) when used for sciatic nerve block in the rat. As a reference, we compare LPSPs to 60 μm median diameter poly (lactic-co-glycolic) acid (PLGA) microspheres (110,000 MW PLGA, glycolic:lactic ratio 65:35). Four days after injection, both particle types produced acute inflammation within the confines of the injectate, inflammation in adjacent tissues, and myotoxicity. Bupivacaine-free particles did not display myotoxicity, and inflammation in adjacent tissues was reduced. At two weeks, inflammation from LPSPs had almost

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disappeared, while PLGA microspheres had a foreign-body giant cell reaction until at least 8 weeks after injection. In contrast, 3.6 μm median diameter, 20,000 MW PLGA microspheres produced a primarily histiocytic reaction 2 weeks after injection. In summary, the LPSPs and PLGA microspheres studied here have excellent biocompatibility, but tissue reaction to the former is of much shorter duration. Myotoxicity and inflammation of surrounding tissue is largely due to bupivacaine. Foreign body giant cells may be due to particle size rather than a specific reaction to PLGA.

Prolonged duration local anesthesia from tetrodotoxin-enhanced local anesthetic microspheres.

Pain. 2003 Jul; 104(1-2): 415-21.

There is interest in developing prolonged duration local anesthesics. Here we examine whether tetrodotoxin (TTX) can be used to prolong the block from bupivacaine microspheres with and without dexamethasone. Rats received sciatic nerve blocks with

75 mg of microspheres containing 0.05% (w/w) TTX, 50% (w/w) bupivacaine and/or 0.05% (w/w) dexamethasone. 0.1% (w/w) TTX microspheres were also tested. The carrier fluid contained 1:100,000 epinephrine. Nociceptive and motor blockade of the hindpaw were quantified. Nerves and adjacent muscles were harvested two weeks after injection for histological assessment by light microscopy. The median nociceptive block duration in hours from the microsphere groups were: bupivacaine =

6.2, 0.05% TTX = 0, bupivacaine + TTX = 35.3, bupivacaine + dexamethasone = 31.3, TTX + dexamethasone = 8.1, TTX + bupivacaine + dexamethasone = 221.7. Some animals receiving particles containing 0.05% TTX had deficits in the uninjected extremity; all animals receiving 0.1% (w/w) TTX particles died. Pockets of particles were associated with localized inflammation, and all samples showed some evidence of myotoxicity in the vicinity of the injection. The nerves themselves appeared intact. In summary, coencapsulation of TTX in controlled release devices containing bupivacaine and dexamethasone resulted in very prolonged nerve blocks. As formulated here, this preparation had a narrow margin of safety. While the myotoxicity appears consistent with the well-known reversible myotoxicity associated with local anesthetics, its long-term significance remains to be established.