Otoprotective Pharmacologic Agents:The Way Forward

Kathleen CM Campbell, PhD
Distinguished Scholar and Professor
Southern Illinois University School of Medicine
Springfield, IL

Challenges in Development

- 1) Is the drug designed to protect hearing from aminoglycoside-, cisplatin/carboplatin- or noise-induced ototoxicity?
- 2) What are the financial considerations? What is the intellectual property status?
- 3) How will it be delivered?
- 4) In which species is it safe and effective?
- 5) Has it been used in humans?
- 6) Is it approved by the FDA for other purposes? Are similar drugs approved?
- 7) Which clinical trial populations are available?
- 8) What is the timeline for development?

Which Ototoxic Indication?

The most common indications are aminoglycoside, cisplatin/carboplatin, or noise induced ototoxicity.

Each indication has its special considerations and challenges.

In some cases, it may be desirable that an otoprotective drug work across all areas. For example an immunosuppressed patient on chemotherapy may need an aminoglycoside for a resistant strain hospital infection. Or a soldier with NIHL may also require an aminoglycoside for an infection. Some patients on chemotherapy may be noise exposed at work or recreationally.

A drug that protects against NIHL but exacerbates aminoglycoside induced hearing loss may not be the best drug for all patients.

Challenges for Aminoglycoside Otoprotection Development

- If given systemically, extensive testing is needed in vivo and usually in vitro to determine if the drug interferes with the aminoglycosides bacterial kill. This testing must be done for each aminoglycoside and for a wide variety of target pathogens. The tests are very expensive and time consuming and require specialized labs for infectious agents.
- If the protective agent is given directly to the round window, will it be effective in the presence of otitis media, common in infectious disease populations?
- Aminoglycosides are frequently given over a period of weeks and stay in the cochlea for prolonged periods. How long will the otoprotective agent need to be administered?
- These patients may be fragile and side effects must be minimal.
- The highest rate of aminoglycoside induced ototoxicity is in impoverished countries. Pharmaceutical companies have little financial incentive to develop products for that market and may not be able to recover their development costs.
- Clinical trials in developing countries are challenging. The stringent infrastructure for clinical trials may not be present.
- One focus has been to develop new aminoglycosides with less ototoxicity to reduce the need for a protective agent.

Challenges for Cisplatin/Carboplatin Otoprotection Development

- If given systemically extensive testing is needed to ensure that the otoprotective agent does not reduce or inhibit the tumor kill for the target cancers.
- Are sufficient numbers of patients available? Are targeted patients already committed to studies for other agents? Do you need to go through a cooperative study group?
- If the protective agent is given directly to the round window, will it be effective in the presence of otitis media, common in immunosuppressed populations and children in general?
- These patients can be fragile. Side effects must be minimal. Palatability is critical in nauseated patients.
- Markets could be high. The FDA has incentives for orphan drugs and for pediatric approvals.
- US Clinical trial sites exist, including networks if you can access them.

Challenges in Development for Long Term Noise Induced Hearing Loss

- For many noise exposed populations, the exposure continues for years. Therefore the drug must be safe over a period of years for that type of exposure. Safety data and clinical trials over long periods of time can be expensive and time consuming. Attrition can be high. Patent clocks run out.
- Other factors affecting hearing are likely to impact results over long time periods.
- Same issues for age related hearing loss.

Challenges in Development for Short Term Noise Induced Hearing Loss

- For most of these populations the focus is on reducing exposure and increasing protection: as it should be.
- For blast injury, the populations have highly variable and unexpected exposures rendering it difficult to compare treated and control groups or even to access the population.
- Protective agents are more likely to prevent or treat metabolic rather than mechanical damage.
- Clinical trials in the military have an extra layer of rules and regulations.
- TTS clinical trials may or may not predict PTS protection but even if they do, they may not be sufficient for FDA approval.
- TTS clinical trials inducing TTS for study are controversial.

Systemic Versus Round Window Delivery

- Systemic:
- May have beneficial effects throughout the body such as nephrotoxicity for cisplatin or aminoglycosides.
- If oral, the drug must survive the digestive system and first pass through the liver. Oral bioavailability may be limited by formulation.
- If given iv, extensive testing is need for compatibility with all materials and possible injection site reactions.
- Greater likelihood of systemic side effects.
- Greater likelihood of interfering with patient's other medical conditions or medications.

Round Window or Transtympanic Delivery

- If injected through the round window, how will the amount of drug actually administered to each round window be measured? Round window access can vary by species and in humans by individual.
- If a longer term administration is given by gel, by pump, or other system, will it stay in place? Will the drug migrate through the Eustachian tube affecting other body areas? Could it be swallowed?
- Can it be placed when and in the patients it is needed? (eg. Battlefield injury, at sea, in a small child)
- Does the drug irritate mucosal tissues of the middle ear? Will repeated injections or placement damage the tympanic membrane?
- What happens in the presence of otitis media?
- Will its presence mechanically reduce hearing?
- Will placement in the target population require sedation?
- Who is qualified to place it? (eg medic versus otolaryngologist)

Which species?

- For noise induced hearing loss studies, frequently chinchillas are used because, unlike most rodents, their hearing is very similar to humans. But they have poor renal clearance as a desert animal so cannot tolerate cisplatin or other drugs easily. Suppliers are limited.
- Rats are hardy and used for many cisplatin studies and some noise studies but have a much higher frequency range of hearing than humans.
- Guinea pigs are the most common model for aminoglycosides but pigmented guinea pigs are no longer available for research and albinos are not always the optimal model comparing to pigmented humans.
- Mice have the most defined genetics but the histology is more difficult and a wide variety of strains must be considered for each application.
- If a drug is safe and effective in multiple species, that is a good sign. But you never want to waste animals.
- For the toxicology and pharmacokinetic studies, the standard models for FDA submission are rat and dog. Then these data are also collected in Phase 1 clinical trials with more safety data collected throughout all clinical trials.
- Animal models are essential and form the basis for virtually all of the effective medicines we all use every day.

Has the Study Drug Previously Been Used in Humans? Is it FDA Approved for Another Purpose?

- If a drug has previously been used in humans, that provides an enormous advantage because information in the target species exists.
- If the drug is an FDA approved drug for any purpose that means that both safety and efficacy, at least for one purpose has met the rigorous FDA standards.
- The clinical development program for an FDA approved drug is much easier, even if the drug is for a new purpose. That does not mean that an FDA approved drug can automatically be promoted or used for another purpose but it does mean that the development program for the new application can draw from the existent information.

Is the New Drug Similar to Other Drugs?

- If the drug is of a similar class to other approved drugs, that does not mean it is the same as an approved drug.
- The class of drug may help guide the types of testing needed for the new drug.
- For example a new aminoglycoside or platinum based chemotherapeutic may be required to test for hearing loss in clinical trials even if the pre-clinical animal studies did not show ototoxicity.

What is the Timeline for Development?

- Patents only last 20 years (although some extensions may be available in some cases)
- Considering that developing a new drug through FDA approval may cost more that 2 billion dollars, a sufficient number of patent years need to remain for the company to not just recover its costs and make a profit. The profits will probably also need to cover the drugs they developed that did not get approved.
- Therefore clinical trials extending over many years may not be viable. The time pressure can be high.

Clinical Trials Process

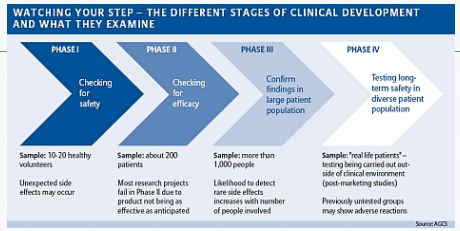

Image from: http://www.agcs.allianz.com/insights/expert-risk-articles/watching-clinical-

Phase I: Checking for Safety

- Small Group (usually 20 – 80) of healthy volunteers
- First human exposure
- Single dose and short-term repeated dose
- Assess tolerance
- May be blinded or open label
- Describe pharmacokinetics (how the body effects the drug) & pharmacodynamics (how the drug effects the body)
- Explore drug metabolism and drug interactions
- Estimate activity
- If a phase 1 study is conducted in the target population is it is referred to as a Phase 1b study and the phase 1 study in healthy volunteers is a Phase 1a.

Adapted from: SOCRA (Society of Clinical Research Associates) presentation, Chicago 2011

Phase O - Microdosing

- Some clinical trials may include a Phase O.
- Small group (10 -15) of healthy volunteers
- Single micro-dose
- Determine if PK and PD profiles are as predicted from pre-clinical research
- Enable researchers to quickly decide which drug candidates will undergo further development
- Little or no safety or efficacy data
- Speeds the development of drugs

Adapted from: SOCRA (Society of Clinical Research Associates) presentation, Chicago 2011

Phase 2: Checking for Efficacy

- Small group (usually 100 – 300) of patient volunteers
- Open label or blinded; usually randomized
- PK studies to assess behavior of drug in patients with target disease
- Assess therapeutic efficacy in patients with target disease
- Define safety profile in patients
- Determine dosage schedules for subsequent studies
- Provide basis for confirmatory studies

Adapted from: SOCRA (Society of Clinical Research Associates) presentation, Chicago 2011

Phase 3: Confirm Findings in Large Patient Population

- Large group (usually 1000 - 3000) of patients with the target indication
- Comparative study with placebo or similar drugs already on the market
- Nearly always blinded or randomized
- Confirm efficacy
- Establish safety profile
- Establish dose/response relationship
- Provide basis for risk/benefit assessment
- Provide support for planned marketing claims

Adapted from: SOCRA (Society of Clinical Research Associates) presentation, Chicago 2011

Phase 4: Testing Long Term Safety in a Diverse Patient Population

- Start this phase after FDA approval
- Real-life patients in a clinical environment
- To optimize the use of the drug with the approved indication
- Evaluate the efficacy and tolerability in this larger very diverse group of patients
- Also called 'Post-Marketing Surveillance Studies'

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Purpose of an IND

- It affirms a body of knowledge about the manufacturing, pharmacology, and toxicology of the drug to support its use in human testing.
- Requires that the clinical investigation be performed in accordance with Good Clinical Practice (GCP).
- Provides an additional level of protection through FDA oversight. The FDA's review focuses on safety of human subjects and ensuring that the studies will produce useful information to assess safety and efficacy of the test product.

Source: Translational Research Program: www.childrenshospital.org/trp

When an IND is Required?

- New drug or biologic product
- New use of an approved drug or biologic
- New use of a combination of an approved drugs or biologics
- Combination products in which the components are physically, chemically or otherwise combined and the primary mode of action is due to the drug or biologic

Adapted from: Louise Johnson, M.S. INVESTIGATIONAL NEW DRUG APPLICATION (IND) Requirements for Filing and Contents of Subm
The Bio2Device Group May 18, 2010

When an IND is not Required for Drugs and Biologics

- Study of placebo
- Study of approved drug or biologic used under the approved label
- When it falls under the DSHEA Act

Adapted from: Louise Johnson, M.S. INVESTIGATIONAL NEW DRUG APPLICATION (IND) Requirements for Filing and Contents of Subr
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DSHEA (Dietary Supplement and Health Education Act) of 1994

- Enacted to "preserve the consumer's freedom to choose dietary supplements"
- Defines dietary supplements as food and not drugs
- Defines permissible labeling claims and places the burden of proof on the FDA to show that a product is unsafe
- Just because a product is in a health food store does NOT mean it is healthy
- Things that are safe at a low dose may NOT be safe at a high dose
- Drug interactions with a patient's other medications or genetics
- Some herbs are toxic: some are deadly
- Natural does not mean safe: arsenic and cyanide are natural
- The DSHEA act does not guarantee package contents
- The DSHEA act does not allow a supplement to be promoted to treat or prevent any disease. (Including hearing loss)

Source: http://www.quackwatch.org/02ConsumerProtection/dshea.html

Questions and Comments