1992 Analgesic Guidance and Current Issues

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Introduction

- **1992 Guideline for the Clinical Evaluation of Analgesic Drugs**
  - **Guidance to analgesic development and research**
  - **Focus on NSAIDs and opioids**

- **Need to resolve major issues**
  - **Emerging new molecular entities**
  - **Growth of knowledge about analgesics and analgesia**

Major areas for improvement in 1992 Guidance document

- **Indications**
- **Chronic studies**
- **Pain models**
- **Dosing**
- **Efficacy parameters**
- **Study controls**
- **Effect/sample size**
- **Safety**
- **Opioid sparing**

92 Guidance - Indications

- **For the management of pain**
- **Evidence for pain of several different etiologies will justify “general purpose” analgesic labeling.**
- **Inclusion of specific labeling indications for preoperative medication, for support of anesthesia, for obstetrical analgesia, or for dysmenorrhea requires specific studies.**

Indications - Current issues

- **General versus specific indications**
  - **The number of acute and chronic pain models**
  - **Representative sub populations**
  - **Major types of pain**
  - **Guidance to practitioners**
  - **Minimizing unsafe and ineffective off-label use**
- **Specific indications**
  - **Unable to study all due to lack of model sensitivity**
  - **Requires unique pharmacodynamic activities**

Indications - Current issues

- **Acute versus chronic indication**
  - **Need to study short-term and long-term efficacy**
  - **Regulatory requirement: model, replication, and length of study**
- **Short-term multiple dose study**
  - **Initial dosing regimen**
  - **Loading dose if necessary**
  - **Optimal dosing interval**

92 Guidance - Chronic studies

The focus of the multiple-dose studies of more than 2 to 3 days in duration is to provide documentation of "clinical acceptability" and safety of the test drug rather than providing pivotal proof of efficacy.

Chronic studies - Current issues

- **Length of long-term studies**
- **Pivotal proof of efficacy**
- **Value for drugs with delayed onset**
- **Off-label use for chronic pain as a problem**
- **Useful information for product labeling**
  - **Long-term benefit/risk ratio**
  - **Durability effect**

92 Guidance - Pain models

- **The selection of pain model depends on strength of analgesia, route of administration, model sensitivities, active control, and mechanism of action.**

- **The initial phase II studies should explore a wide enough range of pain models.**

Pain models - Current issues

- **Need for more acute and chronic pain models**
  - **Limited models for acute pain**
  - **Limited models for chronic pain**

- **Need for models to study the worst pain**
  - **Dosing regimen**
  - **Concomitant/rescue analgesics**

92 Guidance - Dosing

- **Phase II studies "should explore the entire dose-response curve of the test drug and should be the basis for selecting the dose used in later phase II and phase III studies."**

- **Phase III studies are "intended to assess the effectiveness of the recommended dosage schedule under conditions of use."**

Dosing - Current issues

- **Dose levels and dosing intervals**
  - **Dosage obtained from acute setting may not apply to chronic use**
  - **Dosing for optimal benefit/risk ratio versus dosing for convenience**
- **Fixed dosing for establishing efficacy**
  - **Clinical practice versus clinical trials**

92 Guidance - Efficacy parameters

- **“The development program for an analgesic should collect data to describe adequately onset of effect, peak effect, and duration of effect. There are many ways to collect data on these measures of efficacy.”**

- **There is a long list of measured and derived parameters.**

Efficacy parameters-Current issues

- **Choice of efficacy parameters**
  - **Minimize bias**
  - **Time course of effect**
  - **Dosing recommendations**

- **Pain curves, onset, and duration**
  - **Valid and reliable tools**
  - **Acute and chronic settings**

Efficacy parameters-Current issues

- **Chronic pain evaluation**
  - **Pain-related functional status**
  - **Patient global satisfaction**

    (both positive and negative experiences)
  - **Primary versus supportive evidence**

92 Guidance - Study Controls

- **Single-dose study: placebo and active control**
- **Short-term multiple-dose study: active control or placebo control with rescue**
- **Long-term multiple-dose study: active control**

Study controls - Current issues

- **Need for adequate control in both acute and chronic analgesic studies**
- **High placebo response in analgesia trials**
- **Superiority versus equivalence design**
- **Special considerations for chronic studies**
  - **Differential dropout rates**
  - **How to keep blinding intact if different safety profiles**

92 Guidance - Effect/sample size

- **Calculation of sample size "depends on the variance, the magnitude of difference to be detected, and the desired power."**

- **Special consideration should be given to the "validity and the implications of the clinical significance of the differences or similarities to be detected."**

Effect/sample size - Current issues

- **Clinically meaningful effect size**
  - **Debate on definition**
  - **No consensus**
  - **Approach**
  - **Data base**

- **Sample size**

92 Guidance - Safety

- **Peripherally acting or NSAID oral analgesics: regular dosing for at least 6 months**
- **Centrally acting oral analgesics: regular dosing for at least 1 month, continuing for at least 3 month if feasible**
- **Oral combination analgesics: regular dosing for at least 1 month**

Safety - Current issues

- **Extent of exposure and adverse events**
- **Need to study the maximum dosing proposed**
- **ICH guidelines for chronic pain**
  - **Minimum number of subjects**
  - **Minimum length of exposure**
- **Representative study population**
- **Special population with high risks**
- **Large safety trial if serious concerns**

Opioid sparing - Current issues

- **Clinical relevance of opioid sparing**
- **Extent of dose sparing to be clinically meaningful**
- **Concurrent analgesics**
  - **Standardization**
  - **Data analysis combining pain data and rescue**
- **Adjuvant analgesics**
- **How to evaluate efficacy and safety**

Conclusions

- **Many issues to be resolved**
- **Need for updating 92 Guidance document**
- **Need for proposals for future analgesic research**
- **Need for consensus among researchers, drug sponsors, and regulatory agency**