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White Paper

PHARMACEUTICAL

Analgesic Agents and Strategies in Pain Research

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1. Introduction

Pain is a major primary health care problem with an enormous impact on public health. Pain is the most common symptom for which patients seek medical attention[1, 2] and is a major cause of sick leave[3]. It is estimated that a third of the population lives with chronic pain, defined as pain lasting longer than six months, including about 100 million Americans[4].

Although there is no exact definition of pain it can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage[5]. Despite intense research there has been a lack of real breakthroughs in novel analgesic drug development over the past fifty years. Current drug treatments for pain either work poorly or are associated with dose-limiting adverse effects which severely curtail their use, including gastrointestinal bleeding with nonsteroidal anti-inflammatories (NSAIDs)[6]; drug dependency, tolerance and respiratory depression with opioids[7]; and urinary retention, blurred vision, dry mouth with tricyclic antidepressants[8].

The combination of high prevalence and a lack of satisfactory treatments means that there is significant unmet medical need for new medicines for the treatment of pain. This is reflected by the fact that, at the time of writing, there are more than 3432 on-going trials and among them 416 are industry-sponsored interventional clinical trials related to the pharmacological treatment of pain[9]. Regulatory authorities in Europe and North America have responded by recently issuing updated draft guidance on clinical development of products for the treatment of pain[10, 11].

2. Challenges of Clinical Trial Design

Designing clinical trials for the testing new medicines for the treatment of pain is a very challenging area. Pain is a subjective phenomenon and typically acute pain in the postoperative period decreases over days, while the chronic pain of osteoarthritis can wax and wane over weeks. To further complicate matters a high and variable placebo response rate is common.

In the United States the FDA typically expects sponsors to conduct two separate placebo-controlled trials, while in Europe the EMA will not accept two-arm placebo-controlled trials if a proven intervention is available. In addition, in dose-response studies at least three fixed doses of active treatment plus a placebo arm are normally required. These challenges can be addressed by the Dental Impaction Pain Model.

3. Dental Impaction Pain Model (DIPM)

Pain following removal of impacted third molar tooth is a useful clinical model for evaluating pharmacological treatments for pain, particularly those targeted at acute pain. The modern version of the Dental Impaction Pain Model (DIPM) was developed in the mid-1970s[12] and today it is arguably the most utilised of all the acute pain models. It is particularly useful for proof-of-concept studies that require dose-ranging and profiling of the time-effect curve for efficacy including onset, peak effect, and duration of analgesic activity[13]. In addition the DIPM can test analgesics across a range of modes of action, differentiate between numerous treatments arms (of comparator drugs or dose levels), demonstrates high levels of reproducibility, and give results that can be generalised to other pain states. For this reason the DIPM has been included in the regulatory submission of many analgesic products which have been approved by the FDA, EMA and other authorities internationally.

Sensitivity of the DIPM

Many studies have defined the exceptional sensitivity, reproducibility, and versatility of the DIPM. The assay sensitivity of DIPM is such that clear-cut separation of active drugs from placebo has been demonstrated with a sample size of just ten per group[14].

Such exquisite sensitivity is due to the homogeneity of the study population, the predictable level and appropriate intensity of the postsurgical pain, and the minimisation of variability by using a single study centre[13].

Versatility of the DIPM

The DIPM is significantly more versatile than other pain models. The model can be easily adapted to perform multiple-dose studies and to correlate pharmacodynamics to pharmacokinetics (PK/PD modelling). The model can also be used to investigate pre-emptive interventions where the investigational drug is given pre-operatively. In addition, the possibility of a single site being able to enrol all required subjects in an acceptable timeframe ensures variability between centres is eliminated.

The DIPM has been used to evaluate NSAIDs (both selective and nonselective COX inhibitors), opioids and combination analgesics, as well as investigational drugs with unique mechanisms of action. As the underlying pathophysiology of pain becomes elucidated the DIPM will continue to serve as a tool for monitoring the relative contributions of different pain events, including peripheral and central sensitization[12].

Logistical Factors

Logistical and demographic factors also favour the use of the DIPM in pain studies. For example, study subjects are usually young and otherwise healthy, without pre-existing pain or complicating medical illnesses. In addition the number of available subjects is large.

Potential subjects are typically present on an elective waiting list and scheduling can be somewhat flexible to allow time for well-planned screening and pre-operative procedures. The surgical procedure is short, well standardised and typically completed without use of sedation and using only local anaesthesia. This ensures subjects are alert and ambulatory immediately after surgery, without memory impairment or drug-induced nausea. These factors, coupled with the overall intensity and temporal distribution of pain (onset two to four hours post-operatively, remaining relatively constant for twelve hours before diminishing gradually over the next one to two days) have led directly to the popularity and widespread acceptance of the DIPM.

4. Tools for Assessing Pain Intensity

Pain intensity is the fundamental measure that defines the efficacy of an analgesic drug. As patient-reported outcomes, pain intensity can be measured by numerical rating scales, visual analogue scales, or categorical scales.

Visual Analogue Scale (VAS)

The VAS is a continuous variable and uses a 10 cm line to register a score from “no pain” to “Worst pain imaginable” (Figure 1). Patients are asked to indicate by drawing a single vertical line on a paper the point along the line that best represents their pain intensity at the time of the assessment. The distance of the line along the scale constitutes the pain intensity.

Figure 1 - Visual Analogue Scale

Verbal Rating Scale (VRS)

Participants use a 4-point categorical verbal rating scale for the subjective assessment of post-operative pain. The VRS is collected as an independent measure of the patient’s pain, separate to that recorded on the VAS.

Participants are provided with a worksheet and are asked to select the word that best describes their level of pain by checking the appropriate box from None[(0)] to Mild[(1)], Moderate[(2)], or Severe[(3)]. The number associated with the adjective chosen by the participant constitutes the pain intensity.

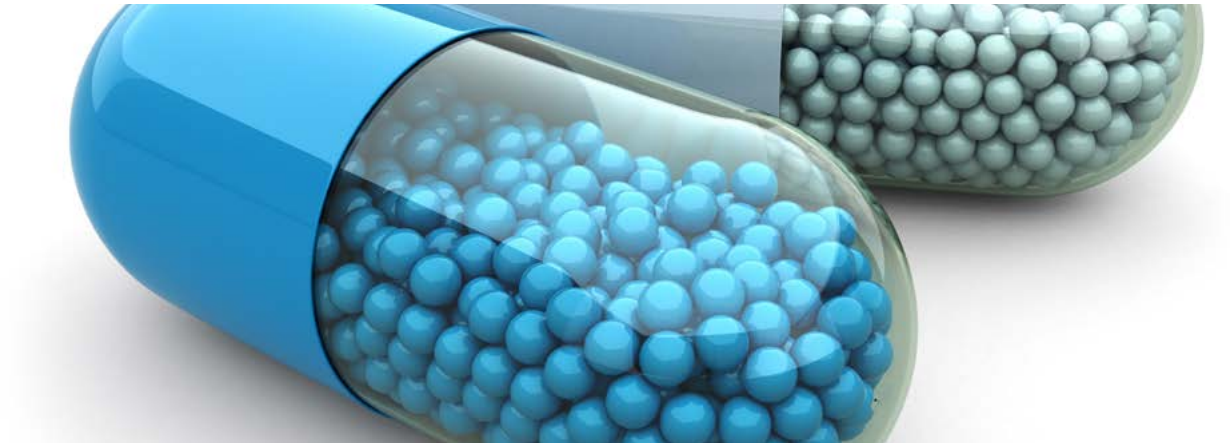
5. Tools for Pain Relief Assessment

Verbal Rating Scale (VRS)

Participants use a 5-point categorical verbal rating scale for the subjective assessment of post-operative pain relief. Participants are provided with a worksheet and are asked to check the appropriate box that best describes their level of pain relief from None (0), Slight (1), Moderate (2), Lots (3), or Complete (4). The number associated with the adjective chosen by the patient constitutes the pain relief.

Global Evaluation

Global assessments aim to elucidate the subject's integrated, overall experience with the analgesic, rather than an additional assessment of efficacy or safety. They are sometimes used as exploratory endpoints to use when interpreting change using other measures. At either the completion of the evaluation period or at the time the subject takes a rescue analgesic, whichever comes first, participants are provided with a worksheet and are asked to check the appropriate box that best describes how they would rate the study medication they received from Poor (0) to Fair (1), Good (2), Very Good (3), or Excellent (4). The number associated with the adjective chosen by the patient constitutes the global evaluation.



6. Duration of Analgesic Effect (Time to first rescue medication)

For this measure, VAS and VRS scores are completed immediately prior to dosing with rescue medication and the time at which rescue medication is administered is recorded.

Double-stopwatch Method

The onset of action of the test medication is determined by noting the time of any pain relief and then time to meaningful pain relief.

This is achieved using the double-stopwatch method as follows: when the local anaesthesia following surgery has dissipated, and the patient's pain is of moderate or severe intensity, the appropriate rating is recorded on the patient self-evaluation questionnaire as the baseline pain intensity assessment. At that time, the patient is given two stop watches and told to stop the first one when they start to feel any pain relieving effect, and to stop the second watch when meaningful pain relief is achieved. Measures of pain intensity and pain relief are recorded at each time point.

7. The Centro Ricerche Cliniche di Verona

The Centro Ricerche Cliniche di Verona (CRC), operated by CROMSOURCE, conducts acute dental pain clinical trials using the DIPM.

The versatility and sensitivity of the DIPM, coupled with the modern facilities at CRC, allows rapid assessment of potential new analgesic drugs in a range of proof-of-concept and efficacy studies. Our reputation for successful compound separation with the DIPM is well established and acknowledged by major pharmaceutical companies.

The CRC is custom designed to conduct high-volume trials and complex protocols with equipment at the clinic including an ECG, -70°C freezer and refrigerated centrifuges, secure investigational drug storage and customer monitoring rooms. In addition, proven operational and quality control systems maintain data integrity and quality assurance.

The CRC and the DIPM

These acute dental pain studies are performed in patients previously scheduled for extraction of at least one fully or partially impacted, third mandibular molar tooth. Surgery is performed at the CRC under local anaesthesia by board-certified maxillofacial oral surgeons from Verona University. The surgery waiting list is used to match otherwise healthy volunteers to a study protocol. Patients enrolled into a study are required to visit the CRC on at least three separate occasions: screening, surgery and study treatment day and for a follow-up visit. In this manner CRC can recruit more than 20 patients per month and more than 420 in total, either as outpatients or as inpatients.

The CRC has proven expertise in simple[15] and complex study designs using the DIPM, including randomised, double-blind, double dummy, parallel group, placebo- and active-controlled, single- or multiple- dose design clinical studies.

As an example, an acute pain study may compare the analgesic efficacy of two drugs given as fixed combinations together with the analgesic efficacy of each single component in comparison[16]. This can be achieved in a single study using ten treatment arms: four different fixed combinations of the two test drugs, four corresponding single treatments, placebo, and ibuprofen as an active control. The experience of CRC in complex designs such as this ensures successful completion of such projects.

Dosing may be also performed before or after surgery. With post-operative dosing, patients who complain of moderate to severe pain on the VRS within three hours of surgery are randomised to treatment. Alternatively, patients can be dosed preoperatively, generally within one hour of surgery. In this scenario, patients allocated to active comparator receive a second dose of ibuprofen (400 mg), 4 hours after the first 800 mg dose, while patients in the test drug and placebo groups receive placebo at this time. Pain intensity and pain relief assessments, safety assessments and pharmacokinetic sampling can all be undertaken pre-dose and up to 24 hours post-surgery. Again, CRC has experience of both models of dosing.

8. Conclusions

Pain is a major primary health care problem and there is major unmet medical need for new medicines for the treatment of pain. Designing clinical trials for the testing new medicines for the treatment of pain is a very challenging area. The Dental Impaction Pain Model (DIPM) is widely utilised and is particularly useful for proof-of-concept, dose-ranging and efficacy studies for analgesic drugs. The Centro Ricerche Cliniche di Verona (CRC), with CROMSOURCE support, is very experienced at conducting trials using the DIPM and use of the centre allows rapid assessment of potential new drugs.

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10. About The Authors

Stefano Milleri has over 25 years' experience of senior level roles in clinical development, experimental medicine and clinical pharmacology unit management. Before joining Centro Ricerche Cliniche di Verona (the CROMSOURCE Early Phase facility) in 2006 as Scientific and Medical Director, Stefano was for many years the Director of the Clinical Pharmacology & Discovery Medicine (CPDM) Unit for GSK in Verona.

Stefano received his MD and specializations in Lung Disease and Geriatrics from Universita' Cattolica del Sacro Cuore in Rome, and his PhD in Neuroscience from Padua University and is a fellow of the Italian Society of Pharmacology. He is also a visiting professor, teaching courses at the universities of Verona, Florence, Milan and Pisa and is co-author of more than 20 full papers published in peer reviewed journals and 40 conference abstracts/proceedings.

Crispin Bennett is a medical writer for CROMSOURCE, based in the Stirling (UK) office. With a PhD in biochemistry, Crispin has over twenty years of industry experience working on new drugs in novel therapeutic areas, taking projects from study design and protocol writing through to the final study reports.

About CROMSOURCE

CROMSOURCE is an ISO-certified international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialised in clinical development and staffing solutions.

CROMSOURCE was founded in 1997. Its successful growth over the last 20 years has been built on stability, integrity, and high levels of customer satisfaction, all of which contribute to a high rate of repeat business. We have grown steadily, but responsibly, to become an organisation of over 550 organised and well-trained experts.

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CROMSOURCE Quality
ISO 9001:2015 multi-site certified quality management system
ISO 14155:2011 conformity confirmed

European Headquarters
Via Giorgio De Sandre, 3
37135 Verona - Italy
Direct: +39 045 8222811

North American Headquarters
309 Waverley Oaks Road, Suite 101
Waltham, MA 02452 - USA
Direct: +1 617.871.1128

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