CHDR
Centre for Human Drug Research

PainCart®

Multi-modal, standardised pain test battery

PainCart: a multi-modal, standardised test battery

PainCart is a comprehensive battery of tests for studying the efficacy of analgesic compounds against several types of pain, including thermal, electrical, chemical, and mechanical pain.

A clear advantage of PainCart is its fully mobile format, allowing researchers to perform the complete battery of tests while on the go. Moreover, the built-in software ensures consistent testing and reliable data capture, handling, and storage.

Practical answers to important research questions

Does our compound have the desired analgesic effect?

At CHDR, we maintain a database of PainCart profiles for a wide range of analgesics, including ketamine, fentanyl, ibuprofen, paracetamol, buprenorphine, paracetamol, and several experimental compounds. This database allows use to compare the effects of a new substance with these existing profiles.

Studies performed at CHDR confirm that this approach is highly successful. For example, researchers used PainCart to show that a compound targeting the nerve growth factor (NGF) pathway - a new class of potential analgesics - has a clear therapeutic effect and a profile similar to ibuprofen, revealing anti-inflammatory properties. This approach can also help with the selection of patients for follow-up studies. Importantly, PainCart can also be used to predict whether a putative analgesic compound might not work in clinical studies.

What is the optimal dose?

PainCart also excels at providing important information regarding dosage, particularly when paired with other test batteries such as NeuroCart. For example, although NeuroCart demonstrated that a given dose of a GABA-A receptor agonist had a pharmacological effect, PainCart revealed that this dose did not provide sufficient analgesia; however, at higher doses, the expected analgesic effect was observed.

Does our analgesic compound interact with other CNS drugs?

PainCart can also be used to study synergistic and/or other interactions between two analgesic compounds, or between an analgesic and another CNS drug (for example, an antidepressant); this provides researchers with a powerful strategy for reducing the analgesic dose and/or uncovering harmful drug-drug interactions. For example, CHDR used PainCart to measure synergy between two compounds - a selective noradrenaline reuptake inhibitor and an opioid analgesic - in the treatment of neuropathic pain.

‘A database of PainCart profiles allows use to compare the effects of a new substance with these existing profiles.’

PainCart highlights

- High inter-subject and intra-subject consistency and repeatability
- Mimics a wide variety of pain mechanisms
- PainCart profiling provides one of most robust measures of analgesic efficacy
- The tests can be repeated many times, providing pharmacokinetics information
- Both single and multiple ascending dose studies can be performed

Validation and clinical relevance

PainCart has been thoroughly validated by studies that focussed on characterising well-known analgesics. PainCart can also support preclinical hypotheses regarding the compound’s putative mechanism of action and clinical efficacy. Importantly, PainCart is just one of several powerful tools used by CHDR to predict the clinical effects of novel drugs.

For more information regarding all of our services, as well as our ongoing research programme to increase the predictive value of PainCart and other tools, visit www.CHDR.nl.

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PainCart:
a closer look

Cold pressor test
Used in clinical studies to investigate cardiovascular responses and nociception. In this test, the subject first places an extremity (usually a hand) into a warm water bath for 2 minutes with a slightly inflated blood-pressure cuff on the upper arm. After 2 minutes, the subject transfers the extremity to an ice-cold water bath. The test ends when the subject's pain tolerance threshold is reached (or 2 minutes have elapsed, whichever comes first).

Thermal pain test
A thermode attached to the subject's skin is used to vary temperature intensity, and sensory thresholds such as heat- or cold-induced pain can be measured.

Inhibitory conditioned pain modulation
The descending supraspinal pain inhibitory pathways are responsible for modulating pain induced in one part of the body but perceived in another part of the body. These pathways are impaired in many patients with chronic pain. Inhibitory conditioned pain modulation is studied by measuring a subject's electrical pain tolerance threshold before and after the cold pressor test (the conditioning stimulus).

Electrical pain test
An electrical stimulus is applied to the skin on the lower leg. The current is increased in 0.5-mA increments each second, and the subject rates the pain using an electronic visual analogue scale (VAS). The test ends when either the subject's pain threshold or the maximum safe stimulus is reached, whichever occurs first.

Test	Pain Stimulus	Domain/Mechanism/Receptor Tested
Thermal pain	Thermode	TRPV1 (>42°C, capsaicin) TRPV2 (>53°C)
Electrical pain	Transcutaneous electrodes	Nociceptors
Tourniquet pain	Pneumatic pressure	Deep muscle nociceptors
Cold pressor	Cold water bath (1°C)	TRPV3 (<17°C)
Inhibitory conditioned pain modulation	Alternating between the cold pressor test and electrical pain test	Supraspinal inhibitory control over ascending pain stimuli
Capsaicin-induced hyperalgesia	Topical capsaicin and thermode	Inflammation, TRPV1
Thermal grill illusion	Interlaced heat and cold	Central (thalamic) pain control mechanisms
UVB hyperalgesia	UVB irradiation and thermode	Inflammation

TRPV, transient receptor potential vanilloid; UVB, ultraviolet B

Tourniquet test
Pressure pain induction is a model for 'deep' muscle pain. This test primarily assesses nociception generated from the muscle with minimal contribution from cutaneous nociceptors.
An inflatable tourniquet cuff is placed over the calf, and the pneumatic pressure is increased steadily while the subject rates the pain intensity using an electronic VAS. The test ends when the subject's pain threshold is reached or maximum pressure is achieved, whichever occurs first.

Thermal grill illusion
The thermal grill illusion test is used to model some of the features of neuropathic pain. The test model is believed to cause a paradoxical sensation of burning by disinhibiting noxious cold-sensitive afferents in nociceptive pathways at the thalamo-cortical level.

The subject places the palm of the hand on a series of alternating warm and cold bars (which on their own are not painful), and the sensation (a combination of thermal intensity, pain intensity, and unpleasantness) is rated using a VAS.

UVB hyperalgesia
UVB irradiation is used to induce localised 'sunburn', thus providing a model of inflammatory pain. Mild erythema is induced on a small patch of skin using UVB irradiation. As a result, thermal pain perception is intensified in the affected area (primary hyperalgesia) and in the surrounding (unaffected) area (secondary hyperalgesia). A thermode is then used to measure changes in thermal pain detection threshold.

Capsaicin-induced hyperalgesia
This model is widely used to mimic certain elements of neuropathic pain by chemically activating TRPV1 channels. The subject's skin is heated, and topical capsaicin is applied. The skin is re-sensitised with heat in order to maintain the model for several hours, and any changes in erythema, spontaneous pain, allodynia, and hyperalgesia are measured.

Profiling secondary effects

Because most analgesics have effects beyond simply reducing pain, a thorough analysis of these secondary effects is important for ensuring the safety of subjects in clinical studies and may also provide additional information regarding a compound's mechanism of action. Another battery of tests called NeuroCart can be used concurrently with PainCart. NeuroCart includes a series of neurocognitive and neurophysiological tests that can be used to measure various neurological systems before and after administration of a test compound. More information is available at www.CHDR.nl and in the NeuroCart brochure and fact sheet. In addition to PainCart and NeuroCart, CHDR offers resting-state functional MRI (RS-fMRI), which can provide researchers with information regarding the site and mechanism of action of a CNS drug.

Respiratory depression is a potentially severe secondary effect of many opioid analgesics. The dynamic end-tidal forcing (DEF) method, developed in Leiden, allows researchers to study how opioids and other centrally acting compounds affect respiratory function.

Why choose CHDR?

The Centre for Human Drug Research specialises in early-phase clinical drug research. CHDR's overall mission is to improve the drug development process by collecting as much information as possible regarding the candidate drug in the early phases of development. This information helps sponsors make informed decisions regarding the course of clinical development for their product.

Why choose CHDR?

Research at CHDR covers a wide range of fields, including the central nervous system (CNS) and pain, the cardiovascular system, haemostasis, immunology, and dermatology. In addition, CHDR is at the forefront in developing novel biomarkers and methods for measuring drug-related effects in all of these research areas.

Pharmacology matters

Whether studying a new cognitive-enhancing drug, a next-generation painkiller, or a new monoclonal antibody designed to treat rheumatoid arthritis, the goal is to determine how the compound's effects correlate with both the dose and blood concentration at any given moment. In addition, understanding which biological systems are activated is an essential first step towards quantifying this relationship. At CHDR, our focus on pharmacology is reflected clearly in what we call question-based drug development.

Question-based drug development

CHDR actively uses question-based drug development - or QBD - as a more rational approach to drug development compared to conventional approaches. QBD can be best described as a series of questions that are addressed throughout the process. These questions often seem simple enough, but failing to answer even one question - or even addressing the questions in the wrong order - can have dire consequences. Thus, using this approach can potentially save companies millions of dollars by helping predict a catastrophic issue early in the development process, before the more expensive latter stages (for example, large-scale clinical trials or the marketing phase).

From a general perspective, the most important questions are:

1. Does the biologically active compound and/or active metabolite(s) reach the intended site of action?
2. Does the compound cause its intended pharmacological and/or functional effect(s)?
3. Does the compound cause any unintended pharmacological and/or functional effect(s)?
4. Does the compound have a beneficial effect on the disease and/or clinical pathophysiology?
5. What is the compound's therapeutic window?
6. How does any variability with respect to the drug response in the target population affect the product's development?

Contact us

Would you like to learn how PainCart can help you quickly obtain accurate, reliable pain data? Or would you like to find out about other services CHDR has to offer?

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