CHDR
Centre for Human Drug Research

NeuroCart®

NeuroCart: the next generation of multifunction, standardised CNS test batteries

NeuroCart is a full battery of tests for measuring a wide range of CNS functions. Importantly, NeuroCart can be used to correlate a compound's CNS effects with drug concentration, helping determine whether an effect is due to specifically the compound.

A clear advantage over other CNS test batteries is that NeuroCart provides both objective (e.g. neurophysiology) and subjective (e.g. cognitive function, memory, mood, etc.) measures of CNS function. In addition, NeuroCart is completely mobile and self-contained, including all of the necessary equipment and protocols.

Practical answers to important research questions

Does our compound have the specific properties that we expect?

CHDR performed the first-in-human trials to test a short-acting benzodiazepine. Researchers used a NeuroCart test (saccadic peak velocity) and determined the dose that produced the same effect as a standard dose of midazolam. Pharmacokinetics/pharmacodynamics (PK/PD) analyses showed that the new benzodiazepine was more potent and faster acting than midazolam. Importantly, the predicted optimal dose, potency, and duration of the new compound were subsequently confirmed in clinical studies with patients.

How do we determine the optimal dose?

Because NeuroCart's neurophysiological tests can be used as a surrogate marker for measuring a drug's effect, these tests can be used to identify a dose that has the same effect on CNS function as the effective dose of a known compound.

For instance, CHDR recently studied a new neuroleptic D2 receptor antagonist. Using NeuroCart, and the adaptive tracking test in particular, researchers were able to determine a dose with similar potency as an effective dose of haloperidol. Importantly, although previous studies predicted an effective dose of 60 mg, NeuroCart showed that a much lower dose (10-30 mg) is effective. Clinical research in patients later confirmed that a dose as low as 5 mg dose is effective, and fewer adverse effects were reported at this lower dose compared to 60 mg.

How do we steer between effect and complications?

In some cases, preclinical research can provide evidence that a promising candidate drug may have a relatively small therapeutic index, as in the case of an ORX1/2 antagonist, a new sleep-inducing medication. Researchers worried that this new drug might induce a narcolepsy-like state, particularly at higher doses. To test this possibility, CHDR used several NeuroCart tests and found that this new compound has promising properties similar zolpidem and is safe at a dose of 1 mg. These findings were later confirmed in clinical testing.

'Does your compound do what you want it to? What is the optimal dose that provides maximum results with the fewest side effects? NeuroCart can answer these questions and more.'

NeuroCart Highlights

- A comprehensive battery that can test all functional domains of the CNS
- Provides both objective and subjective measures
- Rapid retesting allows researchers to complete several rounds of testing both before and after the drug is administered
- Full dose-effect curves can be measured quickly and easily
- High sensitivity can robustly detect even subtle effects
- The highly flexible design can be adapted easily to meet a sponsor's specific needs
- Test data are captured automatically and entered directly into a CDIS-validated system
- The tests are safe and have been used successfully for nearly three decades to test a wide range of CNS drugs

Validation and clinical relevance

Because NeuroCart has been validated thoroughly in healthy volunteers using a wide variety of established CNS drugs, NeuroCart results can help support preclinical hypotheses regarding a compound's effects and mechanism of action. Importantly, NeuroCart is just one of several powerful tools used by CHDR to predict the clinical effects of a novel CNS drug.

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

'NeuroCart is the most thoroughly validated test battery for measuring "proof-of-pharmacology" of CNS drugs.'

NeuroCart: a closer look

Objective tests

Saccadic eye movement
Saccadic eye movements are highly sensitive and specific measures of the subject's alertness, sedation and tranquillity. Saccadic peak velocity is one of the most sensitive measures of alertness currently available in drug research. The subject is instructed to continuously look at a dot of light on a computer screen. As the dot 'jumps' from side to side on the screen, the eyes' movements are monitored.

Functional domain	Test or measure
Alertness	Saccadic eye movement
Visuomotor coordination	Adaptive tracking
Motor coordination	Smooth pursuit eye movement
	Body sway
General CNS activity	Electroencephalography (EEG)
Sleep	Polysomnography
Autonomic nervous system	Pupil size
Subjective drug effects	Visual analogue scale (VAS)
	Questionnaires
Memory	Memory tests
Cognitive performance	Cognitive tests

Adaptive tracking
Adaptive tracking measures visuomotor coordination and vigilance. Adaptive tracking is particularly sensitive to drugs that can induce ataxia. In this test, the subject uses a joystick to move a small dot so that it stays within a continuously moving circle on a computer screen. During the test, the speed of the circle is adjusted in response to the subject's ability to keep the dot in the circle, ensuring that the test is adapted to the individual subject.

Smooth pursuit eye movement
Measuring smooth pursuit eye movements provides a measure of the subject's coordination. In this test, the subject is instructed to follow a dot of light with the eyes as the dot moves smoothly from side to side on a computer screen.

Body sway
The body sway test measures the subject's body movements in a single direction (usually forward/backward movement). Body sway is measured while the subject stands with his/her eyes closed, similar to the Romberg test.

Electroencephalography (EEG)
Pharmacology coupled with EEG recording can be used to quantify 'general' effects of CNS drugs. At CHDR, various EEG approaches can be performed, depending on the compound being tested and sponsor's specific needs, and include EEG recordings based on International Pharmaco-EEG Society (IPEG).

Polysomnography (PSG)
With polysomnography, a panel of physiological parameters is recorded continuously throughout the night in order to measure sleep objectively. PSG is used to monitor various sleep characteristics and sleep architecture. PSG generally includes EEG, electrooculography (EOG), electromyography (EMG), electrocardiography (ECG), and respiration measurements.

Pupil size
Measuring pupil size in real time provides a simple, reliable measure of the autonomic nervous system. Using standardised digital photography, both pupils are measured repeatedly. The resulting images are then scored independently in the context of a clinical research protocol.

Subjective tests

Memory testing
Testing the effects of a CNS drug on memory can be difficult. Memory is often reduced during sedation, and it may appear to be impaired by drugs that affect other systems. Therefore, memory tests should be used in combination with other NeuroCart tests in order to minimise the risk of these complications.

Memory relies upon several key steps in information processing: acquisition, storage, consolidation, and retrieval. The content of memories (e.g. visuospatial, verbal, etc.) is also important. Therefore, NeuroCart was designed to measure all of these aspects of memory. For drugs that affect memory specifically, a more extensive set of tests can be used.

Cognitive tests
Cognitive impairment is common among neuropsychiatric disorders, but can also arise as a side effect of CNS drugs. The cognitive tests in NeuroCart are designed to identify a drug's effects on cognition and to identify potentially confounding non-cognitive factors such as sedation and low motivation. The following cognitive tests are included in NeuroCart (others can be added at the sponsor's request):

- The Sternberg's Memory Test (SMT) is a working memory task designed to measure the retrieval of information from recent memory.
- The Symbol Digit Substitution Test (SDST) assesses visual perception and other cognitive functions regarding attention, short-term memory, and psychomotor speed.
- The Dual Task (DT) test is designed to measure how much mental workload a subject can handle. In this test, the participant is instructed to perform an acoustic task and a visual task with varying stimulus onset asynchrony (SOA). As SOA become shorter, interference between the two tasks increases.
- The Stroop test provides information regarding attention, perception, and the cognitive and neural mechanisms that underlie mental inhibition.
- The Choice Reaction Time (CRT) test is a parametric version of the Stroop test. Left/ right distraction is an executive task that is affected by processes that can influence mental flexibility.

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

To learn how NeuroCart can help you quickly obtain accurate, reliable CNS data, and to learn about our full range of services, contact us today.

+31(0)71 524 64 00

info@chdr.nl

www.chdr.nl