

CNS-K-01 — PMT STUDY CLONIDINE SUPPRESSION TEST PROTOCOL IN BRIEF: INSTRUCTIONS FOR BLOOD SAMPLING AND DATA COLLECTION

- Drug dosage:**
- Clonidine – given orally at a dose of 0.3 mg (60-80 kg patient) or 4.3 micrograms per kilogram for patients outside this weight range.
- Preparation:**
- Test to begin in the morning after an overnight fast (clear fluids-water allowed).
 - No paracetamol for 4 days before testing.
 - No children or pregnant women
- Blood Samples:**
- Blood 10 mL lithium-Heparin-Monovette, e.g., SARSTEDT 02.1065.001
 - Collected blood samples are immediately placed on ice or cool packs and maintained cold (4°C) at all times during storage and transport to the laboratory.
- Procedure:**
- Subjects supine throughout the entire test period with an indwelling i.v. for blood sampling and i.v. fluids as required.
 - Baseline blood pressure and heart rate measured 3 times and recorded in the data collection sheet.
 - Baseline blood sample taken after 30 minutes of supine rest and immediately before administration of clonidine.
 - Time of clonidine administration and drug dose recorded in data collection sheet.
 - Blood pressure and heart rate monitored continuously with single measurements recorded in the data collection sheet at 1 hour and 2 hours post clonidine.
 - Test blood sample taken at 3 hours (180 minutes) after clonidine, with time of the blood sample recorded in the data collection sheet.
 - Blood pressure and heart rate are measured and recorded in triplicate in the data collection sheet, immediately after the 3-hour test blood sample is drawn.
 - **Blood samples must be transported to the laboratory immediately after collection of the final 3-hour test sample** (Instructions for laboratory staff are provided separately).
- Data collection:**
- The attached data collection sheet should be filled in by the study nurse on each occasion the clonidine suppression test is carried out.
 - In addition time, blood pressure and heart rate, recordings must also be maintained of all complications during the test as indicated in the data collection sheet.
 - Should the test need to be canceled, this should be stated and the complication outlined as indicated in the protocol worksheet.
 - Any deviations from the protocol must also be explained and recorded in writing on the data collection sheet which must be forwarded to the supervising clinician at the completion of the study.

See also the third page for more detailed instructions and information about test principles, test interpretation, drug interactions and other precautionary considerations.

PMT STUDY DATA COLLECTION SHEET — CLONIDINE SUPPRESSION TEST

Name: _____ Unique ID: _____ Date: _____

Baseline Blood Pressures (mmHg) and Pulse (bpm)

BP No. 1: _____ No. 2: _____ No 3: _____

Pulse No. 1: _____ No. 2: _____ No 3: _____

Time Clonidine administered: _____ Dose: _____

BP 1 hr: _____ Pulse 1 hr: _____ BP 2 hr: _____ Pulse 3 hr: _____

Time 3 Hour post-clonidine blood sample taken: _____

Three Hour Post Clonidine Blood Pressures (mmHg) and Pulse (bpm)

BP No. 1: _____ No. 2: _____ No 3: _____

Pulse No. 1: _____ No. 2: _____ No 3: _____

COMPLICATIONS:

- | | | |
|---------------------------------------|--|-------------------------------------|
| <input type="checkbox"/> Dry mouth | <input type="checkbox"/> Ringing in the ears | <input type="checkbox"/> Confusion |
| <input type="checkbox"/> Flushing | <input type="checkbox"/> Lightheadedness | <input type="checkbox"/> Drowsiness |
| <input type="checkbox"/> Headache | <input type="checkbox"/> Fainting | <input type="checkbox"/> Tiredness |
| <input type="checkbox"/> Nausea | <input type="checkbox"/> Vomiting | |
| <input type="checkbox"/> Other: _____ | | |

Check the box if test canceled or of there was any deviation from protocol

If any box is checked provide written explanation here: _____

TEST DETAILS: USE OF PLASMA NORMETANEPHRINE AS AN END-POINT MARKER FOR THE CLONIDINE-SUPPRESSION TEST

PRINCIPLE: Clonidine activates α_2 -adenergic receptors in the brain and on sympathetic nerve endings to suppress noradrenaline release by sympathetic nerves, but is without effect on catecholamine release from pheochromocytomas. The clonidine-suppression test was originally developed to distinguish whether high levels of plasma noradrenaline reflect increased release by sympathetic nerves or release by a pheochromocytoma. The test can similarly be used to distinguish whether high levels of plasma normetanephrine result from metabolism of noradrenaline released by sympathetic nerves or from metabolism of noradrenaline within a pheochromocytoma.

The test is particularly useful in patients where initial testing of plasma free metanephrines yields elevations of normetanephrine that are of insufficient magnitude to unequivocally establish the diagnosis of pheochromocytoma (e.g., plasma levels above 112 pg/mL and below 500 pg/mL). This represents the range of values where it can be particularly difficult to distinguish a true-positive result from a false-positive test result.

TEST INTERPRETATION: Pheochromocytoma is confirmed when normetanephrine remains above the upper limit of normal (112 pg/mL) and fails to fall by more than 40%. Pheochromocytoma is excluded by either or both a fall in plasma normetanephrine after clonidine to below 112 pg/mL or by more than 40% (relative to baseline levels).

PRECAUTIONS: Before the test is implemented, consideration should be given to possible causes of false-positive test results for measurements of plasma normetanephrine (e.g., seated posture when blood sampling, physiological stress and clinical conditions leading to increased sympathetic nerve activity, drugs such as tricyclic antidepressants). When possible, such causes of false-positive results should be excluded before further testing is carried out.

The clonidine suppression test should not be carried out in any patient taking tricyclic antidepressants or other drugs that would either compromise test results or that are contraindicated because of potential interactions. Patients typically become hypotensive starting one hour after the drug is taken. Severe hypotension may occur in some patients, particularly those taking beta-blockers or who have a history of postural dizziness or orthostatic intolerance. Blood pressure and pulse rate should therefore be monitored throughout the test. Large decreases in blood pressure may be treated using i.v. fluids and legs elevated according to the Trendelenburg procedure.

Patients should be instructed to remain supine throughout the test; if changing from the supine to the seated or to the standing position is unavoidable, patients should be advised to carry out such changes slowly, and with assistance. A family member should be available to escort the patient home after the test. The patient should not drive for at least 12 hours after the test or until symptoms of the drug (e.g., drowsiness, dizziness) disappear.

LIMITATIONS: While the test has very high diagnostic specificity (a positive result – i.e., lack of suppression - strongly indicates a pheochromocytoma), false negative test results are possible for patients with slightly increased baseline levels of normetanephrine (e.g., 112-150 pg/mL). While the test is useful for distinguishing true-positive from false-positive elevations of normetanephrine, it cannot be used for distinguishing true-positive from false-positive elevations of plasma metanephrine.