International multicenter observational study to determine the diagnostic sensitivity of plasma metanephrines and urinary catecholamines and metabolites compared to standard evaluation procedures in children with high risk neuroblastoma

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Primary objectives:To demonstrate that diagnostic sensitivity of plasma metanephrines (free and total) is superior to standard evaluation procedures (urinary Dopamine, HVA and VMA) at diagnosis and end-of-induction assessment.Secondary objectives:•…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Observational invasive

Summary

ID

NL-OMON51513

Source
ToetsingOnline

Brief title
Metanephrines

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
malignant tumor from the sympathetic nervous system, Neuroblastoma

Research involving
Human

Sponsors and support

Primary sponsor: Centre Hospitalier Universitaire Vaudois-CHUV
Source(s) of monetary or material Support: Loterie Romande;Villa Joep

Intervention

Keyword: Neuroblastoma, Plasma metanephrines, Urinary Catecholamines

Outcome measures

Primary outcome

Sensitivity of plasma metanephrines (free and total MN, NMN, MTX), compared to standard evaluation procedures (urinary Dopamine, HVA, VMA) at diagnosis and end-of-induction in children with high risk neuroblastoma.

Secondary outcome

• Sensitivity of plasma metanephrines (free and total MN, NMN, MTX) compared to eight metabolites (VMA, HVA, 3MT, dopamine, E, MN, NE and NMN) in urine at diagnosis and end-of-induction in children with high risk neuroblastoma.

• Sensitivity of plasma metanephrines (free and total) compared to other gold standard diagnostic and monitoring tools (MRI, MIBG scan, bone marrow evaluation), at diagnosis and end-of-induction.

• Sensitivity of free and total plasma metanephrines and urinary catecholamines and metabolites at end of induction in correlation to age at diagnosis, disease stage, histology and molecular characteristics.

Study description

Background summary

Neuroblastoma is the third most frequent tumor in children after leukemia and brain tumors and is the most common cancer in infants.
Various tools are used to diagnose neuroblastoma and monitor its response to treatment, including the assessment of urinary excretion of catecholamines and its metabolites. The currently used biochemical diagnostic criteria were established on the basis of an international consensus: the urinary dosage of dopamine and its metabolites VMA (vanillin-mandelic acid) and HVA (homo-vanillic acid) is considered the gold standard for diagnosis and biochemical monitoring of the disease. However, catecholamines and the HVA/VMA metabolites remain insufficient indicators for the diagnosis and therapeutic follow-up of neuroblastomas. Data from Strenger et al. confirmed a sensitivity of 80.7% for the measurement of dopamine alone and 91.2% for the combination of dopamine, VMA and HVA. Recently Verly et al performed a retrospective urine analysis in 301 neuroblastoma patients at diagnosis, measuring a total of 8 metabolites for diagnostic accuracy (VMA, HVA, 3-methoxytyramine [3MT], dopamine, epinephrine [E], metanephrine [MN], norepinephrine [NE] and normetanephrine [NMN]), and obtained an overall 89% sensitivity for NMN as single diagnostic metabolite, and a 95% sensitivity when combining all 8 metabolites.
Moreover, studies on pheochromyocytoma, another tumor originating from the neural crest and producing large amounts of metanephrines, showed that the measurement of plasma metanephrines and in particular free metanephrines are currently considered as the gold standard diagnosis tool for pheochromocytoma.
In patients with neuroblastoma, Peitzsch and al. showed that the diagnostic sensitivity of 97.9% of 3MT or NE in plasma, in 94 patients, was significantly higher than the diagnostic sensitivity of HVA and VMA in urine. A specific feature for neuroblastoma is that these tumors secrete dopamine and its methoxylated metabolite methoxytyramine. We postulate that plasma methoxytyramine is a more sensitive biomarker than plasma dopamine because it is produced directly by the tumor, is not reuptaken by receptors and exhibits a longer half-life than dopamine. In addition, another advantage would be the replacement of the urinary spot or inaccurate 24-hour urine collection in young children by a blood sample taken during routine blood analysis.
In order to evaluate diagnostic significance of plasma metanephrines in patients with neuroblastoma, we first established in a prospective study in a cohort of 191 healthy children, boys and girls, aged 0-18 years, nonexistent reference range curves for full baseline values for free and total plasma metanephrines. In addition, we examined plasma metanephrines in 10 patients who were routinely diagnosed with neuroblastoma. Total and free NMN and 3-MT showed to be the best parameters with a 100% sensitivity at diagnosis
In conclusion, a prospective study is needed to confirm and establish the role of new urinary and plasma biomarkers at diagnosis, follow-up and detection of residual disease/relapse, applying a well-established, harmonized and approved method of measurement to reduce variability between laboratories and to pick

out the most significant marker/s for future clinical use.

Study objective

Primary objectives:
To demonstrate that diagnostic sensitivity of plasma metanephrines (free and total) is superior to standard evaluation procedures (urinary Dopamine, HVA and VMA) at diagnosis and end-of-induction assessment.

Secondary objectives:
• To evaluate whether diagnostic sensitivity of plasma metanephrines (free and total) is equal/superior/inferior to urinary catecholamines and metabolites at diagnosis and end-of-induction assessment.
• Correlate plasma metanephrines (free and total) and urinary catecholamines and metabolites to outcome (end-of-induction remission) and compare to other gold standard diagnostic and monitoring tools.
• Correlate plasma metanephrines (free and total) and urinary catecholamines and metabolites to different disease subgroups, such as age at diagnosis, disease stage, histology and molecular characteristics.

Study design

International multicenter prospective study
Duration: 2 years

Study burden and risks

This study enters the *A*very low risk category as it entails no more than minimal risks and burdens for the participant. Indeed, the study procedure (blood drawn for plasmatic dosage of metanephrines) will be performed during a routine blood collection and will not require any additional venipuncture. Specific analyses in urine will be performed on samples taken from routine assessments.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

• Patients with confirmed high risk neuroblastoma (clinical and/or biological)
• Patients treated within or according to SIOPEN HR-NBL-2 clinical trial
• Age < 18 years at inclusion, male or female
• Ethic committee approval for each participating site
• Informed consent signed by the legal representatives and/or by the child according to local regulations

Exclusion criteria

• Renal insufficiency (creatinine clearance according to Schwartz formula < 60ml/min/m2)
• Absence of histological confirmation of high risk neuroblastoma
• Lack of consent

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-07-2022
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	16-06-2022
Application type:	First submission
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL80132.041.22