Pheochromocytoma randomised study comparing adrenoreceptor Inhibiting agents for preoperative treatment (PRESCRIPT)

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The primary objective is to determine which of two commonly used drugs for preoperative management provides the best intraoperative hemodynamic control in patients undergoing resection of a PCC. Secondary Objective(s): o to identify other…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Adrenal gland disorders
Study type	Interventional

Summary

ID

NL-OMON41372

Source
ToetsingOnline

Brief title
PRESCRIPT

Condition

- Adrenal gland disorders
- Endocrine neoplasms benign

Synonym
pheochromocytoma - tumor which produces stresshormones (epinephrine and norepinephrine)

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Ipsen Farmaceutica BV (unrestricted grant)

Intervention

Keyword: doxazosin, hemodynamic control, phenoxybenzamine, pheochromocytoma

Outcome measures

Primary outcome

The main study parameter is defined as the number of patients demonstrating

more than three intraoperative episodes of 5 minutes with blood pressure

outside the predefined target range after pretreatment with either

phenoxybenzamine or doxazosin.

Secondary outcome

o success rate of doxazosin and phenoxybenzamine to attain preoperative blood

pressure target values without co-medication

o resolution of (paroxysmal) symptoms and signs

o need for additional antihypertensive agents

o adverse effects of study medication

o length of preoperative period with use of study drugs in either outpatient

or inpatient clinic

o distribution frequency of germline mutations associated with PCC

o control of blood pressure and heart rate a. during surgery: b.

postoperatively during stay at intensive or medium care (at least 24 hours)

- number of episodes with systolic blood pressure (SBP) > 160 mmHg

- number of episodes with mean arterial blood pressure (MAP) < 60

mmHg

- duration (in minutes) of SBP > 160 mmHg

- duration (in minutes) of MAP < 60 mmHg

- number of episodes with heart rate > 100/min

- duration (in minutes) of heart rate > 100/min

- amount and type of vasoactive agents needed during surgery for

adequate blood pressure control

- cumulative amount and type of intravenous fluids administered

o length of postoperative stay at intensive/medium care unit

o length of hospital stay

o composite semi-quantitative score of intra- and postoperative hemodynamic

control based on the following parameters:

- blood pressure and heart rate outside target range

- need for administration of vasoactive agents

- need for administration of intravenous fluids

o measurement of NT-proBNP levels before PCC resection

o postoperative hypoglycaemia: frequency and severity (in mmol/L)

o perioperative mortality (i.e. death from any cause occurring during period

from first administration of study medication until 30 days after surgery)

o perioperative cardiovascular morbidity, i.e. cardiovascular events

occurring during period from first administration of study medication until 30

days after surgery. Cardiovascular events are: myocardial infarction, cardiac

arrhythmia requiring medical intervention, heart failure, cerebrovascular

ischemia, cerebrovascular haemorrhage

o composite endpoint of perioperative mortality and perioperative

cardiovascular morbidity

Study description

Background summary

Pheochromocytoma (PCC) is a rare but clinically important catecholamine secreting neuro-endocrine tumour that typically arises from the adrenal gland. In addition, this neuro-endocrine tumour can also originate from chromaffin cells in sympathetic ganglia. In the current study protocol, PCC refers to both adrenal and extra-adrenal chromaffin tumours with hypersecretion of catecholamines (i.e. norepinephrine and/or epinephrine). Data on the incidence and prevalence of PCC in the Netherlands have not been published. Based on the Dutch registry of pathology diagnoses (PALGA), we found an incidence of 117 cases of PCC in the year 2007 (unpublished observation).
PCCs may occur as part of an autosomal dominant inherited tumor syndrome, caused by germline mutations in the RET proto-oncogene (Multiple Endocrine Neoplasia type 2 syndrome), VHL gene (von Hippel-Lindau disease), NF1 gene (Neurofibromatosis type 1), or in one of the genes encoding the subunits of mitochondrial complex II, also called succinate dehydrogenase (SDHB, SDHC, SDHD). PCCs are termed *sporadic* when the family history for PCC is negative. Recent studies, however, have demonstrated germline mutations in one of the PCC susceptibility genes in a significant number of patients with a sporadic PCC, with mutation rates varying between 7.5 - 14.6% in the populations studied. Therefore, genetic testing is recommended in all patients with PCC. Novel PCC susceptibility gene have recently s been described, and it seems likely that future research will result in the discovery of other genetic mutations associated with PCC.
PCC constitutes a surgically curable cause of hypertension.
Hypertension in patients with PCC can be either persistent or paroxysmal, but is absent in a minority of patients. It is a potentially life-threatening disease with a high risk for cardiovascular complications such as myocardial infarction, arrhythmias, cardiomyopathy, stroke and pulmonary edema. The clinical picture results from release of catecholamines by the tumour. This release can be evoked by stimuli that would normally not pose a hazard, such as surgery or general anaesthesia. Thus, preoperative treatment with alfa-adrenoceptor antagonists is usually recommended for prevention of these serious and potentially fatal complications.
Historically, the noncompetitive and nonselective alfa-adrenoceptor antagonist phenoxybenzamine has been the drug of choice. Alternatively, doxazosin - a competitive and selective*alfa1-adrenoceptor antagonist - might be at least as effective as phenoxybenzamine with fewer side effects. Notably,

it has been suggested that doxazosin results in a significant and clinically relevant reduction of postoperative hypotension. Severe postoperative hypotension necessitates admission to the intensive care unit (ICU), where volume resuscitation and norepinephrine are administered under strict monitoring of hemodynamics. Data on the optimal preoperative pharmacological management of patients with PCC are conflicting. Available studies thus far have all been retrospective in design and suffer from several limitations in methodology such as lack of randomisation, use of historical controls and non standardized intraoperative care. Until now, prospective randomised controlled trials comparing phenoxybenzamine and doxazosin have not been conducted. Thus, the preoperative drug therapy of choice remains an unresolved issue, and at a recent international PCC symposium it was concluded that no specific recommendations can be made on this subject. We performed a survey among all university medical centers in the Netherlands, showing that almost half of the centers prescribed phenoxybenzamine, whereas the other centers used doxazosine as the preoperative drug of choice for patients with PCC. Usually, these drugs are administered during 2-3 weeks before surgery. This preoperative medical preparation takes place either in the outpatient or inpatient clinic, depending on patient-related factors (e.g. disease severity, geographical considerations) and local experience.
Preoperative volume expansion is recommended in all patients with PCC.
The rationale behind this recommendation is based on the notion that PCC is associated with a decreased intravascular volume, which is restored under influence of treatment with alfa-adrenoceptor antagonists. Without administration of volume expansion severe hypotension might ensue. Therefore, it is common practice to advise a liberal salt intake during alfa-adrenoceptor antagonist therapy and to administer a saline infusion (e.g. 2L NaCL 0.9% in 24 hours) shortly before surgery.
Several drugs, including certain anaesthetics, may evoke an uncontrolled catecholamine release with resulting severe hemodynamic instability. Patients are advised to carry a document enlisting all medications which are contra-indicated in case of a PCC. There is no consensus on the optimal anaesthetic management during resection of a PCC, as randomised controlled trials on this subject are not available.
PRESCRIPT represents the first randomised controlled trial comparing the effects of pretreatment with either phenoxybenzamine or doxazosin on the intraoperative hemodynamic control in patients with PCC. In addition, PRESCRIPT provides a unique opportunity to prospectively collect data containing detailed information on items such as presenting symptoms and signs, perioperative outcome and results of biochemical, imaging and genetic studies in patients with PCC. Of interest, results of this study are expected to have a direct impact on national and international guidelines regarding the perioperative care of patients with PCC.

Study objective

The primary objective is to determine which of two commonly used drugs for

preoperative management provides the best intraoperative hemodynamic control in patients undergoing resection of a PCC.

Secondary Objective(s):
o to identify other determinants of intraoperative hemodynamic control. Potential determinants are: gender or age of the patient, clinical setting for preoperative management (i.e. outpatient or inpatient clinic), preoperative levels, of catecholamines or N-terminal pro-brain-type natriuretic peptide (NT-proBNP) PCC size, sporadic or hereditary PCC,
o to describe prospectively symptoms and signs of PCC in a large cohort of patients. Note: until now, data on symptoms and signs have been described retrospectively
o to describe prospectively the results of several diagnostic techniques
o to assess prospectively the distribution of sporadic and hereditary PCC in a large cohort of Dutch patients
o to build a biobank with blood and tissue samples for future studies on PCC

Study design

Randomised open-label controlled trial.

Intervention

Not applicable.

Study burden and risks

Participating patients are not exposed to any additional risks, as PRESCRIPT merely compares the efficacy of two frequently prescribed alfa-adrenoreceptor antagonists. In addition, diagnostic work-up and clinical management are almost completely similar to current clinical practice, except for a limited number of extra measurements.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700 RB
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700 RB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

o age > 18 years
o diagnosis of benign PCC (adrenal or extra-adrenal, sporadic or hereditary)
- elevated plasma and/or urinary (nor)metanephrines
- localisation of PCC by anatomical (MRI/CT) and functional imaging (I123-MIBG scintigraphy or 18F-DOPA PET)
o planned for surgical removal of the PCC
o size of PCC on anatomical imaging =/ > 1 cm in diameter

Exclusion criteria

o age < 18 years
o malignant PCC, i.e. presence of lesions on imaging studies suggestive of distant metastases
o severe hemodynamic instability before surgery necessitating admission to intensive care unit
o pregnancy
o incapability to adhere to the study protocol

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-01-2012
Enrollment:	134
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	cardura
Generic name:	doxazosin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	dibenzyran
Generic name:	phenoxybenzamine

Ethics review

Approved WMO

Date:	21-12-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	18-04-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	23-01-2012
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-11-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2010-022417-25-NL
ClinicalTrials.gov	NCT01379898
CCMO	NL33608.042.10