Prevention of progression of duodenal adenomas to cancer in patients with familial adenomatous polyposis.

Published: 21-11-2008
Last updated: 06-05-2024

In the Netherlands, approximately 500 patients with FAP have been recognized, who are at high risk for developing duodenal carcinoma. Better insights in the pathogenesis of duodenal cancer and development of chemoprevention strategies are of pivotal...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Benign neoplasms gastrointestinal
Study type	Interventional

Summary

ID

NL-OMON32335

Source
ToetsingOnline

Brief title
Duodenal adenomas and cancer in patients with FAP.

Condition

- Benign neoplasms gastrointestinal

Synonym
Adenomatous polyposis coli; hereditary polyp disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: KWF Kankerbestrijding projekt KUN 2008-4198

Intervention

Keyword: Celecoxib, Duodenum, Familial adenomatous polyposis, Ursodeoxycholic acid

Outcome measures

Primary outcome

1. Intervention study: number and size of duodenal adenomas.

2. Observational study: duodenal mucosal cell proliferation and apoptosis at two different sites of the duodenum of FAP patients and controls.

Secondary outcome

1. Intervention study: To establish the effects of the intervention on mucosal cell proliferation and apoptosis rates at both sites of the duodenum and in the adenomas, as well as on expression levels of COX-2 and detoxification enzymes.

2. Observational study:

-in duodenal mucosa; measurement of mucosal biotransformation enzymes and expression of COX-2 in patients with FAP as well as in controls

-in duodenal bile; measurement of cytotoxicity and genotoxicity in duodenal bile of patients with FAP and controls.

Study description

Background summary

Familial adenomatous polyposis (FAP) is an autosomal dominant disease, associated with mutations in the APC gene and characterised by the development of numerous adenomas in the gastrointestinal tract, especially in the large bowel. When untreated, this will lead to colorectal cancer early in life. A

prophylactic colectomy is the treatment of choice. As a result, patients grow older and subsequently up to 90% of patients develop adenomas in the duodenum, with increasing duodenal cancer risk, which at present is the main cause of death in these patients. Duodenectomy is the only curative treatment for duodenal cancer, but due to its complexity, mortality and morbidity are high. A promising future treatment may be chemoprevention of carcinomas by cyclooxygenase-2 (COX-2) inhibitors such as celecoxib, which has been shown to slow down or inhibit duodenal or colorectal adenomatosis in patients with FAP. Normal tissue homeostasis requires a proper balance between cell proliferation and apoptosis and COX-2 is a key enzyme in these processes. In the adenoma-carcinoma sequence of FAP, up-regulation of cell proliferation and down-regulation of apoptosis plays an important role. Since in many sporadic colon cancer cases, APC mutations are also present, this suggests that the mechanism of carcinogenesis may have common pathways in sporadic colorectal cancer and FAP. Strikingly, within the duodenum, adenomas cluster around the ampulla of Vater, suggesting that luminal factors, such as cytotoxic bile acids, pancreatic juice or other toxins in bile may trigger duodenal cell proliferation in patients with FAP. Adjunct to COX-2 inhibitors, treatment with ursodeoxycholic acid, which has been shown to reduce cytotoxicity of bile, and may lead to recurrence of colorectal adenomas with high-grade dysplasia, may be an option in patients with FAP. When toxins (in bile) are involved in stimulation of adenoma growth, up-regulation of the mucosal detoxification potential could also be beneficial. Thus, modulation of mucosal (cell proliferation and apoptosis, COX-2, detoxification enzymes such as glutathione S-transferases and UDP-glucuronosyltransferases) and luminal (bile) factors may be of pivotal importance in the search for (new) chemoprevention strategies of duodenal adenomas and carcinomas in patients with FAP.

Study objective

In the Netherlands, approximately 500 patients with FAP have been recognized, who are at high risk for developing duodenal carcinoma. Better insights in the pathogenesis of duodenal cancer and development of chemoprevention strategies are of pivotal importance for these patients. In addition, studies on the interaction of the intestinal content and mucosal cell homeostasis may yield new insights with respect to FAP related duodenal cancers

Study design

1. Chemoprevention trial. A randomized placebo-controlled multicenter clinical trial will be performed on eighty patients with FAP and duodenal adenomas (Spigelman stage II and III), by administration of either celecoxib (400 mgbid) + placebo, or celecoxib (400 mgbid) + ursodeoxycholic acid (25mg/kg/day) for 6 months. Pre- and post intervention biopsies (two sites: near ampulla and more distal duodenum) and duodenal bile will be sampled. Also biopsies from adenomas will be taken. Primary endpoint will be the effect of the intervention on the

number, size and degree of dysplasia of duodenal adenomas. Secondary endpoints will be the effects of the intervention on mucosal cell proliferation and apoptosis rates at both sites of the duodenum and in the adenomas, as well as on expression levels of COX-2 and detoxification enzymes. In addition, pre- and post intervention bile will be studied with respect to composition, genotoxicity and cytotoxicity.

2. Observational study. Forty patients with FAP in whom endoscopic inspection of their duodenum takes place in Nijmegen at least once a year will be included in this study. Six biopsies of duodenal mucosa near the ampulla, and 6 biopsies from the more distal duodenum will be taken. In addition, duodenal bile will be collected. Duodenal biopsies and bile will also be collected from 40 non-FAP controls, matched for age and gender. Analyses: A) The duodenal mucosa of the patients will be
compared at two sites with that of non-FAP controls for: rates of cell proliferation and apoptosis; levels of COX-2 and detoxification enzymes B) Bile of patients with FAP as well as bile from non-FAP controls will be analysed for composition and concentration of bile acids and fatty acids. In addition, genotoxicity and cytotoxicity will be quantified in the bile samples of patients and controls

Intervention

The chemoprevention study will be a randomised double-blind placebo controlled trial with two arms; each arm including at least 40 patients with FAP. The study design is depicted in Figure 1. Patients with a history of gastric or duodenal ulcers, a prior allergic reaction on NSAIDs or UDCA or disturbed renal- or liver functions will be excluded. Moreover patients with cardiovascular risk factors will also be excluded. No NSAIDs or UDCA may have been used during enrolment.

An upper gastrointestinal endoscopy will be performed with an oblique viewing instrument (Olympus TJF-160), at which number and size of duodenal adenomas will be counted. The procedure will be videotaped and photograph images will be taken of the ampulla, areas of dense polyposis, and areas of mild or no disease, for later assessment. The endoscopist will be unaware of the therapy the patient is receiving. At this endoscopy, 6 biopsies from the normal appearing mucosa in the papillary region as well as 6 biopsies from the distal duodenum will be taken. By staining with indigo-carmine normal mucosa can be differentiated from adenomatous tissue. Moreover, bile will be collected after a CCK bolus.
The patients will be randomised in two groups. Group I will receive celecoxib, 400 mg twice daily and placebo according to the scheme in Figure 1. Group II will receive celecoxib 400 mg twice daily and UDCA (25mg/kg body weight) in a double blind fashion. After six months, a second endoscopy, with collection of biopsies and bile will be performed (Figure 1). At endoscopy, the size and number of adenomas will be counted (primary endpoint) as outlined below.

Figure 1. Scheme outlining the chemoprevention study.

Month 1 2 3 4 5 6

Duodenal biopsies x x
Collection of bile x x

Group I
Celecoxib + placebo x x x x x x

Group II
Celecoxib +
ursodeoxycholic acid x x x x x x

Study burden and risks

All patients will be informed by a Gastroenterologist about the burden and possibel complicatiions of the duodenoscopy, Moreover all patients wille be informed about possibel side-effects of the CCk injection to contract the gallbaldder . Endoscopies will be carreid out by experienced Gastroenterologists.

* FAP patients in the intervention study are under regular surveillance by endoscopy already.
* All participants will sign an informed consent.

Risks:

- Minimal risk of perforation and bleeding by taking biopsies (< 0.1%).
- Minimal risk of pancreatitis by administration of CCK-8 (<1%).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Patients with FAP with duodenal adenomas of Spigelman stage II and III, with an indication for duodenoscopy
-Patients with dyspeptic complaints with an indication for duodenoscopy, but without intestinal abnormalities.
- Age between18-70 years

Exclusion criteria

- Patients with a history of a cardiovascular accident, gallstones, gastric or duodenal ulcers, a prior allergic reaction on NSAIDs or UDCA or disturbed renal (creatinine clearance < 50 ml/min.) or liver function (albumin < 25 g/l or Child-Pugh-score >= 10) will be excluded. No NSAIDs or UDCA may have been used during enrolment.
- Cardiac patients NYHA class II-IV.
- Age below 18 or above 70 years or incapable to sign informed consent

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-02-2009
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Celecoxib
Generic name:	Celecoxib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Ursochol
Generic name:	Ursodeoxycholic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-11-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-11-2008

Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2008-003696-43-NL
CCMO	NL23569.091.08