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Paracetamol & Hepatitis B Vaccination Study

Submission date 26/07/2013	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 14/08/2013	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 09/03/2015	**Condition category** Other	[_] Individual participant data

Plain English summary of protocol

Background and study aims
Paracetamol (acetaminophen) is a medicine that is widely used in children and adults to relieve pain and reduce fever. In many European countries, paracetamol is used after vaccination. In the Netherlands, the advice is to be reserved with the use of paracetamol during vaccination and only children who experienced fever or persistent screaming after vaccination are advised to use paracetamol before further vaccinations. Despite this advice to restrict paracetamol to those children with previous reactions, many parents give paracetamol to their children before or just after the vaccine administrations according to the National Immunization Program (NIP). Paracetamol is generally regarded as safe and is commonly used as an over-the-counter drug. Paracetamol was long considered to be a drug without effects on the immune system. Recently published results suggest a negative influence of paracetamol on the vaccination response. Infants who received paracetamol directly after vaccination to prevent fever had a lower vaccination response. The effects of paracetamol on the immune system could affect the protection level of vaccination. At this moment, it is not known if paracetamol has the same effects in adults. Also, it not known if there is an important role for timing of paracetamol in this effect on vaccination response. It is important to gain insight into the effects of paracetamol use during vaccination. Health organizations should have enough information to offer good advice about the use of paracetamol during vaccination procedures.

Who can participate?
Study participants were healthy young health care students of 18 years or older, who are routinely vaccinated against hepatitis B.

What does the study involve?
This study was composed of two phases. Phase 1 was performed to investigate the effect of paracetamol on the immune response in adults after a hepatitis B vaccination. Paracetamol was taken directly after vaccination to prevent fever and pain after vaccination. Phase 2 was performed to confirm the effects found in phase 1 and to investigate if there is an important role for timing of paracetamol on the immune response to hepatitis B vaccination. Paracetamol was taken directly to prevent and 6 hour after vaccination to treat fever and pain after vaccination. All participants received three doses of the hepatitis B vaccine. Hepatitis B vaccine was given at 0 month, 1 month and 6 months.
Phase 1: Participants were randomly allocated to either an intervention or a control group. The intervention group took two tablets of paracetamol (1000 mg) at three times: directly after the

vaccination, 8 hours after and 16 hours after the vaccination. The control group took no paracetamol. The intervention group took paracetamol during the first and second hepatitis B vaccination, but not during the third hepatitis B vaccination.
Phase 2: Participants were randomly allocated to one of the two intervention groups and a control group. The timing of the paracetamol treatment in the intervention groups was different. One group took two tablets of paracetamol (1000 mg) at three times: directly after the vaccination, 8 hours after and 16 hours after the vaccination. The other group took two tablets of paracetamol (1000 mg) at three times: 6 hours, 14 hours and 22 hours after vaccination. The intervention groups took paracetamol during the first and second hepatitis B vaccination, but not during the third hepatitis B vaccination. The control group took no paracetamol.

What are the possible benefits and risks of participating?
Participants who took paracetamol during the vaccination probably suffered less from side effects of vaccination, such as pain and fever. Participation in this study significantly contributed to scientific knowledge, resulting in a better advice from health organizations about the use of paracetamol during vaccination procedures. There was a possibility that some participants had a reduced protection level at the end of the study. The protection level of every participants was determined and evaluated. None of the participants had a lower protection level. The study population existed of young health care students that were routinely vaccinated against hepatitis B. The vaccination was not an intervention for the students. In the normal hepatitis B vaccination procedure, one blood sample is routinely taken 1 month after the third vaccination. At that moment we drawn 21 ml of blood instead of 5 ml blood. No new injection was needed for this extra blood drawing. An extra blood sample (7 ml) was taken specifically for this study before the third vaccination.

Where is the study run from?
The study was performed at the Hogeschool of Utrecht (The Netherlands).

When is the study starting and how long is it expected to run for?
Phase 1: October 2011 to April 2012 and phase 2: October 2012 to April 2013.

Who is funding the study?
This study was funded by the National Institute for Public Health and the Environment (RIVM) (The Netherlands).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Clinical Trials Information System (CTIS)
2011-000923-33

Protocol serial number
N/A

Study information

Scientific Title
Effects of prophylactic and therapeutic paracetamol treatment during vaccination on Hepatitis B antibody levels

Study objectives
This present study was performed to investigate possible effects of prophylactic and therapeutic paracetamol use in adolescents, on the response to hepatitis B vaccination.
Phase 1: Investigate a possible suppressing effect of prophylactic paracetamol use in adults on the response of the hepatitis B vaccination.
Phase 2: Study the association between timing of the use of paracetamol during hepatitis B vaccination and the development of the immune response in adults.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics review committee of UMC Utrecht. Protocol number 11-170/G-E NL36577.041.11. Approved protocol 14/07/2011, approved amendment 08/08/2012

Study design
Two phases (phase 1 and phase 2) randomized controlled open-label single-centre study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Antibody response after paracetamol use during vaccination

Interventions
The study was performed at the Hogeschool of Utrecht.
In phase 1, one prophylactic and one control group were investigated.

In phase 2, one prophylactic paracetamol, one therapeutic paracetamol and one control group were investigated.
The paracetamol treatment consisted of three doses of paracetamol (two tablets of 500mg) administrated orally within the first 24 hours directly (prophylactic) or 6 hours after (therapeutic) the primary and first booster vaccination. The first administration of paracetamol in the prophylactic group was performed immediately after vaccination in the vaccination clinic. The second and third administrations were done at home every 8h. The therapeutic group took all the administrations at home every 8h.

Control group: no paracetamol allowed for 48h.

All groups have one blood collection (7ml) more than in the normal hepatitis B vaccination procedure directly before the third hepatitis B vaccination.

Follow up of all study participants: first vaccination until the second blood collection (circa 7 months later).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Paracetamol, Hepatitis B vaccine

Primary outcome(s)
Determination of the anti-HBs levels. Blood samples were collected prior (5-6 months after first vaccination) to and one month (6-7 months after first vaccination) after the second booster vaccination in blood collection tubes. Qualitative and quantitative HBsAg antibody levels in the sera were measured on the ADVIA Centaur XP system by using the ADVIA Centaur Anti-HBs assay according to the manufacturer's protocol.

Key secondary outcome(s))
Alterations in the functionality of specific lymphocyte subpopulations in blood of participants that used paracetamol prophylactically or therapeutically. Blood was collected one month (7 months after first vaccination) after the second booster vaccination by using vacutainer cell preparation tubes containing sodium citrate. Peripheral blood mononuclear cells (PBMCs) were isolated from the tubes according to the procedures recommended by the manufacturer. Therafter, B-cells were purified by using the Easysep CD19 kit. Purified B-cells were characterized by FACS-analysis and after polyclonal stimulation memory B-cells specific for HBsAg were detected by ELISPOT. T-cells (PBMCs minus B cell fraction) were stimulated with HBsAg and tested for IFN-gamma secretion by ELISPOT.

Completion date
26/04/2013

Eligibility

Key inclusion criteria

1. Healthy young healthcare students from the Hogeschool of Utrecht, who are routinely vaccinated against hepatitis B
2. 18 years or older, both male and female
3. Written informed consent

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. NSAIDs or paracetamol use within 48 hours before vaccination
2. History of acute or chronic hepatitis B
3. Earlier vaccination against hepatitis B
4. Medical immunosuppressive treatment
5. Primary or secondary immunodeficiency
6. Allergic reaction to components of the hepatitis B vaccination or paracetamol

Date of first enrolment
03/10/2011

Date of final enrolment
26/04/2013

Locations

Countries of recruitment
Netherlands

Study participating centre
RIVM
Bilthoven
Netherlands
3720 BA

Sponsor information

Organisation
National Institute for Public Health and the Environment (RIVM) (Netherlands)

ROR
https://ror.org/01cesdt21

Funder(s)

Funder type
Government

Funder Name
National Institute for Public Health and the Environment (Netherlands)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	04/06/2014		Yes	No