In vivo efficacy of Salbutamol Sandoz versus salbutamol Ventolin GSK in children with asthma

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In this study, we hypothesize that the reference product (SalbR/Ventolin) is more effective than SalbG (Salbutamol Sandoz) atimproving the lungfunction in children with asthma, and that this difference increases alongside the severity of the airway...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational non invasive

Summary

ID

NL-OMON52633

Source
ToetsingOnline

Brief title
Salsa Study

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Asthma

Research involving
Human

Sponsors and support

Primary sponsor: Canisius Wilhelmina Ziekenhuis
Source(s) of monetary or material Support: Longfonds;subsidie CWZ

Intervention

Keyword: children, efficacy, generic, salbutamol

Outcome measures

Primary outcome

- FEV1 after the inhalation of 100 micrograms salbutamol

Secondary outcome

- VAS score after inhalation of 100 micrograms salbutamol

- FEV1 after inhalation of 400 micrograms salbutamol

- VAS score after inhalation of 400 micrograms salbutamol

Study description

Background summary

Since 2016, pediatricians have regularly seen children with an asthma exacerbation, in which case salbutamol Sandoz was used as rescue medication in case of dyspnoea. The subjective impression is often that these children responded less well to this preparation in comparison to before or to the reference product, Ventolin. After switching from the reference product (Ventolin, Salbutamol Reference, SalbR) to generic Salbutamol Sandoz (Salbutamol Generic, SalbG), parents also regularly spontaneously reported that they had the impression of reduced efficacy of SalbG.

Lareb received a striking number of reports in 2016 (63 of which 40 were reports concerning children) regarding an alleged reduced effect of SalbG compared to previous (reference) products containing salbutamol, such as Ventolin and Airomir. These reports mainly came after SalbG became the preferred drug of the Dutch health insurers. In 2015, the concentration of SalbG in the aerosol dose doubled, whilst the release in micrograms would have remained the same, and oleic acid was added (as is also present in other dose aerosols).

Reports received by Lareb came from both healthcare providers and (parents of) patients and did not clearly decrease in the course

of 2016. An inventory via social media by the "LongFonds" clearly displayed the perception of lower efficacy amongst children as well as adults. This also led to a column in the broadcast of EenVandaag.

The CBG has studied and investigated the reports and signals, but has concluded that the quality control as carried out by the EMA was not a reason to remove Salbutamol Sandoz from the market. Various insurers have since accepted other generic products containing salbutamol in dose aerosol as an alternative instead of SalbG.

According to our information, there is currently no other party that will initiate a further in vivo efficacy study of SalbG. Pediatricians suspect Salbutamol Sandoz is less effective than the reference product, thus creating uncertainty and insufficiënt confidence regarding the quality of the product. However, this is essential as patients, parents and healthcare providers must be able to rely on the effectiveness of the "rescue medication".

We consider it conceivable that a different composition of a dose aerosol can lead to a larger particle size (MMAD) and reduced lung deposition. Due to the lower suction power of children, this difference could especially occur with the first 100 microgram inhalation. In other words, the shape of the flow-volume curve differs between children. However, children may also react differently to the full 400 microgram dose. We also consider it conceivable that the registration requirements set by the EMA for the properties of a generic dose aerosol are not strict enough when it comes to administration to children, especially because the product has not been studied in the target group: children with acute asthma. For European registration of generic dose aerosols, it is sufficient if the MMAD particle size is within a range comparable to that of the reference product, and when the biological equivalence (plasma levels) is within a range equal to that of the reference product. The latter is often tested in a small group of healthy adult subjects.
According to the EMA, the registration of a generic inhalation medication for children does not require that the efficacy in vivo (lung function, airway patency) or the bioavailability in children with (acute) asthma be investigated.

SalbG is the most commonly prescribed rescue drug in the Netherlands, so it is likely that many patients experiencing an asthma exacerbation use SalbG. It is therefore unclear whether SalbG is less effective than SalbR, or whether there must be another explanation for the reports.

We consider it necessary for responsible care that rescue medication in children should be proven to be effective in the rescue

setting. To gain clarity regarding the effectiveness of SalbG compared to SalbR, an in vivo study should be conducted in the target group, children with reduced asthma control.

The hypothesis of this study is that the reference product SalbR is more effective than SalbG in improving lung function in children with asthma, and that this difference is greater the more severe the airway resistance is. (Null hypothesis: there is no difference).
This could be explained by different properties and deposition of the aerosol.

Study objective

In this study, we hypothesize that the reference product (SalbR/Ventolin) is more effective than SalbG (Salbutamol Sandoz) at improving the lungfunction in children with asthma, and that this difference increases alongside the severity of the airway resistance.
(Null hypothesis: There is no difference). This could be explained by different properties and deposition of the aerosol.

Purpose of this research:
Rejecting the null hypothesis. This is based on the answers to the questions below.

Research questions:
1. Is there a difference between the increase in FEV1 (and FVC) after 100 µg SalbG versus FEV1 after 100 µg SalbR in children aged 4-14 years with insufficient asthma control? (primary question)
2. Is there a difference in the subjective feeling of the children after inhalation with 100 µg SalbR and after 100 µg SalbG, measured with a VAS score?
3. Is the increase in FEV1 (and FVC) in children with asthma between 4-14 years of age with insufficient asthma control after inhalation of 400 µg SalbR different than after inhalation of 400 µg SalbG?
4. Is there a difference in the subjective feeling of the children after inhalation with 400 µg SalbR and after 400 µg SalbG, measured with a VAS score?

It is generally thought that bronchodilation with 400 µg substantially results in maximal bronchodilation.

Study design

I - Research design
A prospective, randomized, double-blind, comparative study with 2 registered drugs. Only children with a diagnosis of asthma between 4-14 years who undergo a lung function test as part of regular care are

eligible for participation.
After determining whether the patient meets the inclusion criteria and informed consent has has been retrieved, the participants will
be randomized into 4 study arms with different combinations of Salbutamol: They will receive 100+300 µg Salbutamol in the following 4 combinations:

1. SalbG - SalbG
2. SalbR - SalbR
3. SalbG -SalbR
4. SalbR - SalbG.

In each group, 20 children will be enrolled after randomization in blocks (random block size of 4 or 8 children), stratified for the
severity of the airway obstruction measured by the first lung function test (FEV1% predicted for medication). In accordance with
regular care, children will perform a lung function before and after the administration of salbutamol in one of the above
combinations. The total dose of salbutamol administered is 400 µg, the usual dose in regular lung function tests. A low dose of 100
µg is initially administered as this increases the chance of detecting a possible difference in effect on lung function (on the advice of
a delegation of the CBG that was consulted for this). The lung function test usually takes place with video animations so that
children experience it as an attractive game (knocking down cones, blow out candles). The difference with regular care is that the
children undergo an extra lung function test once. This, together with filling in a short questionnaire 3 times, is the extra burden on
the child in the context of this study

II - Setting
The effectiveness is relevant in a critical care situation, meaning that the study should simulate the situation when asthma control is
inadequate (and lung deposition may be reduced). Patients for whom a lung function is performed as part of regular care will be
included. The research will be conducted at the pediatric outpatient clinic of Canisius Wilhelmina Hospital in Nijmegen.

III - Procedure
1. Approach parents/carers and/or the patient who must have a lung function performed as part of regular care by means of an
invitation letter.
2. Send a general letter of invitation via an online asthma platform to approach (parents/caregivers of) the patient, who may be able
to participate in the study.
3. If there is interest, a medical examiner will assess whether the patient has 'doctor's diagnosed asthma'
4. The parents/patient will be contacted by phone to discuss the study and

participation. The PIF is also sent to the parents/patient.
Informed consent is discussed and parents/patients are requested to bring the completed PIF with them to the next outpatient visit.
5. If there is no 'doctor's diagnosed asthma', an email will be sent stating that the patient does not meet the criteria to participate in the study.
6. The (c)-ACT is entered digitally before the outpatient visit by parents/carers and/or patient, if this has not taken place, this is done on paper during the outpatient visit.
7. Determining whether the patient meets the criteria for participation in the study based on inclusion criteria.
8. Register: (c)-ACT and when SABA or LABA was most recently used (regular care)
9. T=0 measurement = 1st VAS score (entered by parent(s)/patient) and lung function (performed by pediatric pulmonary nurse) in the context of regular patient care, in which parent/caregiver/patient, pediatric (pulmonologist) physician and pediatric pulmonary nurse are blinded for the administration of the type of salbutamol.
10. Stratification according to the table based on the baseline FEV1(%predicted) and randomization in blocks of 4, by a doctor's assistant whom is not involved in the lung function measurement: this randomization results in one of the 4 codes and determines which combination of medication the patient will receive.
11. The 1st medication (100 µg salbutamol via VZK Cannister A or B) is to be administered by a doctor's assistant. The doctor's assistant is not blinded to the cannisters. The parent/caregiver/patient, pediatric (pulmonologist) doctor and pediatric pulmonary nurse who will perform further lung function measurements are blinded for the given medication. The cannister is not visible to the patient because it is shielded by a cardboard casing that is positioned around the cannister. The spacer is visible to the patient but will be wrapped so that the aerosol properties are not visible. The doctor's assistant will give the medication as prescribed (https://inhalatorspreis.nl/contents/uploads/iseringsbedrijven/76_1.aerochamber-mondstuk_werkingsmanufactured-20.pdf). The time of administration is noted down in hours and minutes.
12. 2nd VAS score (completed by parent(s)/young person); lung function after T15 = 15 min: MEFV curve exactly 15 min after administration of 100 µg Salbutamol performed by pediatric pulmonary nurse who was not involved in the administration, and is blinded to canisters and randomisation of the patients.
13. Medication administration immediately (< 2 minutes) after measurement: T15, (300 µg salbutamol) administered by a doctor's assistant as before. Time is noted in hours and minutes.
14. 3rd VAS score (completed by parent(s)/young person); T= 30: MEFV curve 15 min after 2nd medication by pediatric pulmonary nurse who was not involved in the administration, blinded to canisters and randomisation of the patients.

15. Afterwards a short questionnaire follows (by a pediatric pulmonary nurse):
1) Does the first puff taste different from the second puff?
2) Does one feel different from the other? If so how?
3) Do you feel that one or the other works better?
4) Does any of the puffs taste like the ones you have at home?
The patient is not shown the lung function data until the entire study protocol, including the questionnaires, has been completed.
This is in order to prevent the data from being influenced.

Study burden and risks

There are no risks associated with participation.

The estimated burden on the patient is considered to be negligible.

The lung function test is performed as a part of regular care. The patient or parents will not have to undergo additional hospital visits. The burden for the child consists of performing one extra lung function test, and answering three short questionnaires about their perceived shortness of breath at the given point in time. The questionnaires will be filled in at 20 minute intervals. There is no difference in the amount of salbutamol used in comparison to a regular visit involving a lung function test, the lung function measurement is the same as in regular care.

Children with asthma generally like the lung function tests, as it is linked to an animation ("computer game", throwing pins, blowing out candles on the screen), and they are familiar with it. The two forms of salbutamol used in this study are registered and are commonly used in the daily practice, both for the treatment of asthma symptoms at home by the patient and parents, as well as in the hospital

Contacts

Public
Canisius Wilhelmina Ziekenhuis

Weg door Jonkerbos 100
Nijmegen 6532SZ
NL
Scientific
Canisius Wilhelmina Ziekenhuis

Weg door Jonkerbos 100
Nijmegen 6532SZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Children (2-11 years)

Inclusion criteria

Inclusion criteria:, - Informed consent of the parents of children up to 12 yrs of age, and informed consent from parents/caretakers of children and of the, children aged 12-14 years., - Children known with doctor's diagnosed asthma, and a history, or physical examanation, or documented positive response on, bronchodilators following lung function testing, indicating reversibility of airways obstruction, - C-ACT (children astma controle test questionnaire 4-11 yrs) or ACT(12-16 yrs) <20 and/or FEV1 decline of at least 15% compared to, personal's best and/or FEV1 < 80 % of predicted value and/or such symptoms that the parents or the physician would administer a bronchodilator

Exclusion criteria

- Severe Asthmatic attack for which high doses of Salbutamol are needed, - Inability to conduct a lung function test reliably, - Inability to read or understand the Dutch Language, - Concomitant other chronic physical or mental condition that precludes conducting a reliable lung function test.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-03-2023
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ventolin
Generic name:	Salbutamol Sandoz
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-10-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-12-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-05-2024
Application type:	Amendment

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	EUCTR2019-000462-38-NL
CCMO	NL67238.091.19