Protocol

PILOT Study/ recruitment: - Randomised Control Trial of asthma risk with Paracetamol vs. Ibuprofen use in infancy

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Background:

The worldwide prevalence of asthma has increased in the past fifty years and there are large differences in prevalence in different countries. The reasons for this are unknown.[1] Better understanding is very important for New Zealand which has one of the highest prevalence rates of asthma and severe asthma in children and adults in the world.[2,3] There is now substantial observational evidence that paracetamol use may represent a novel risk factor both for the development of asthma and increasing its severity once established.

This evidence consists of case-control studies[4,5], cross sectional surveys[6-8] and prospective cohort studies.[9-11] An association between asthma and exposure to paracetamol has been demonstrated in the intrauterine environment[12-17], infancy[6], later childhood[7] and adult life.[4,5,9] The most convincing studies supporting the association between paracetamol and asthma are the GA^{2}LEN Case Control Study in adults[5] and the Phase 3 International Study of Asthma and Allergy in Children (ISAAC).[6,7] The latter showed that the use of paracetamol for fever in the first year of life was associated with an increased risk of asthma symptoms in 6-7 year old children. Current use of paracetamol was associated with a dose-dependent increased risk of asthma symptoms in both the 6-7 and 13-14 year age groups and there was a similar association with the risk of severe asthma symptoms suggesting that paracetamol use may also increase the severity of asthma. However the above association may be confounded by indication as a considerable proportion of paracetamol use in children is for respiratory tract infections, which themselves are associated with an increased risk of asthma.[10,18] There are biologically plausible mechanisms for the association between paracetamol and asthma as paracetamol use depletes circulating and airway glutathione levels leading to increased oxidant-induced inflammation; directly or by enhancing Th2 cell polarization. [19-23]

There is only one published randomised controlled trial (RCT) comparing the effect of paracetamol or ibuprofen use for fever and asthma outcomes in children.[24] This study, a secondary analysis of a larger study investigating the safety of ibuprofen treatment in children with fever, reported that children, who had been treated with acute asthma treatment in the proceeding 24 hours prior to randomisation, had an increased risk of outpatient, but not inpatient, asthma presentation in the following four weeks when randomised to paracetamol compared to ibuprofen for fever management. The increased risk of asthma with paracetamol was dose-dependent and related to respiratory febrile illness rather than other causes of fever. However, this study was in children up to 12 years of age, who were already diagnosed and treated with asthma, and only reported short term risk. What is not available from RCT evidence is the long-term risk of asthma in infants treated with paracetamol in early infancy. This question remains highly relevant to all infants, and to all clinicians who prescribe simple analgesia to infants.

Initially we proposed a randomised open-label parallel group trial of whether paracetamol use, as required for fever and pain, in infants following admission to hospital for bronchiolitis, increased the risk of wheeze and atopy at age 3 compared to placebo. Because paracetamol is so widely used by parents for children for a variety of indications it was difficult to know if parents/guardians will give consent to participate in a study with a 50% chance of randomisation to placebo. So we undertook a feasibility study to determine possible comparators out of ibuprofen, restricted paracetamol (administering paracetamol only if the temperature was greater than 38.5 degrees and / or if the infant was in significant discomfort as recommended by WHO), or placebo. 120 infants were admitted to Wellington Regional Hospital with bronchiolitis during our feasibility study. 72 (60%) parents / guardians completed the feasibility questionnaire. Ibuprofen, restricted paracetamol and placebo were acceptable to 42 (58%), 29 (40%) and 9 (12%) parents/guardians respectively.[25]

While we have established the non-acceptability of placebo and the preferred comparator of ibuprofen in our sample, the feasibility study did raise the question of recruitment sources. We intended to recruit infants admitted with bronchiolitis to maximize the chances of the intended outcome by age three. However, an admission is a stressful time for the family, and it may be inappropriate to ask parents / guardians to consider enrolling their infant in a long term trial. Out of all eligible participants (120) over a single Autumn / Winter period in Wellington, we enrolled 36 (30%) into a 'mini-RCT' comparing paracetamol use with restricted paracetamol use. In the proposed main trial we aim to recruit 1028 participants from 3 main centres. The low recruitment rate seen in our feasibility study would mean we would require a larger number of centres and many years of recruitment to meet our target of 1028 participants. Furthermore, the findings of the study would also only be directly applicable to infants admitted with bronchiolitis and not to all infants who may receive paracetamol

Therefore we now wish to explore the possible recruitment rates of all infants, and as a subset, infants whose first degree relatives have asthma, from three possible domains:

1. At ante-natal classes
2. On the post-natal wards
3. At the 6 week immunization visit at the primary healthcare providers

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Main objective:

1. To establish possible recruitment rates into a proposed main trial of infants randomised to paracetamol or ibuprofen use from 3 possible sources:

    a. Ante-natal classes

    b. Post-natal wards

    c. At the 6-week immunization visit with primary healthcare providers

Outcome variables

Primary:

- Proportion of infants where parents / guardians have indicated they would be likely to enrol them in the proposed main trial

Secondary:

- Proportion of infants whose mother has current asthma where parents / guardians have indicated they would be likely enrol them in the proposed main trial
- Proportion of infants with a first degree family member (mother, father or sibling) with current asthma where parents / guardians have indicated they would be likely to enrol them in the proposed main trial

Study Design

A questionnaire

Study Subjects

In each of the proposed recruitment domains:

1. Pregnant mothers attending ante-natal classes at Wellington Regional Hospital over a three-week period – specific dates to be arranged

2. Mothers and infants on post-natal wards at Wellington Regional Hospital over a three week period – specific dates to be arranged

3. Mothers and infants attending immunisation and 6-week checks at primary health care providers over a three-week period – primary health care providers and specific dates to be arranged

Study Procedures

Pregnant mothers attending ante-natal classes at Wellington Regional Hospital, and mothers and infants either in the post-natal wards, or at the immunisation / 6-week check at their primary health care providers will be approached and given an information sheet about the study. After informed consent, they will be asked to fill out a questionnaire.

The questionnaire will be structured in two parts:

Part 1 – demographics of parents, the infant and family history of asthma, eczema and atopy

Part 2 – the likelihood of parents / guardians enrolling their infant into the proposed main trial of paracetamol as required for pain and fever versus ibuprofen, with an assessment of wheeze and atopy at three years of age.

Power and Statistical Methods

Sample size and Study Power

As this is pilot study, results of this study will help inform sample size and power calculations of the main proposed trial

Statistical methods

Sample proportions for each of the three recruitment domains will be calculated as follows:

1. Proportion of all infants where parents / guardians have indicated they would be likely to enrol them in the proposed main trial
2. Proportion of infants whose mother has current asthma where parents / guardians have indicated they would be likely to enrol them in the proposed main trial
3. Proportion of infants with a first degree family member with current asthma where parents / guardians have indicated they would be likely to enrol them in the proposed main trial

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Safety Monitoring

Adverse Events

As this pilot study involves undertaking a questionnaire only, it is not anticipated that there will be any adverse events associated with this study

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Appendix 1: Design of Proposed Main Trial

Infants from a sample to be determined from this proposed pilot study and / or the already completed feasibility study will be recruited from Wellington, Auckland and Palmerston North Regions.

The Main Trial will be an open label study. Medication will be dispensed by the researchers for use by families who will be asked to use only the experimental medication but to record if they use other treatments. Randomisation will be by a 'third-party' mechanism with internet accessible randomisation codes generated by the study statistician.

After appropriate information and consent from parents/guardians, data collection and randomisation will occur. Exclusion criteria include: families who know they will be leaving the Wellington, Auckland or Palmerston North region in the next 2-3 years, lack of a telephone and infants who have had a hypersensitivity reaction to paracetamol or ibuprofen.

Control group
The planned usual treatment is liberal paracetamol use, as is the current status of paracetamol use in New Zealand.

Intervention group
The intervention groups will be allocated to ibuprofen and will be asked to abstain from using and paracetamol or paracetamol-containing products.

Phone contact will be made with families in the first week after enrolment to monitor use of randomised medication and any identified problems and there-after phone contact at least every three months with a home visit at 18 months and a clinic visit at three years.

Outcome variables:
The primary outcome variable is: symptoms of wheeze in last 12 months at 3 years of age using the ISAAC question[26]: "Has your child had wheezing or whistling in the chest in the last 12 months?" Limiting the question to a 12 month period reduces errors of recall and should be independent of month of completion. This is the most useful question for assessing the prevalence of wheezing illness. This question identifies a mixture of transient, viral and IgE associated wheeze so to increase the specificity for identifying asthma the presence of severe or clinically relevant asthma will be assessed by the presence of wheeze in the last 12 months and one or more of (1) 4 or more attacks of wheezing, (2) sleep disturbance for one or more night per week or (3) speech limitation. The specific questions are: How many attacks of wheezing has your child had in the last 12 months?; In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?; In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?

Secondary outcome variables:
(1) Atopy as measured by a positive skin prick test[27] at 3 years of age: Skin prick tests will be carried out for common allergens: *D pteronysssinus,* cat, mixed grasses, mould, egg, wheat, milk, peanut, and positive (histamine) and negative control (glycerine). Atopy is defined as at least one positive response.
(2) Eczema prevalence at 3 years of age**.** Eczema prevalence at 18 months and 3 years will be defined according to modified UK diagnostic criteria.[28,29] Eczema severity will be assessed using SCORAD.[30]

Data collection
Enrolment data collection will be: Identifying details: (name, address, telephone number, date of birth); birth order, maternal smoking in pregnancy; maternal paracetamol use in pregnancy; birth weight, gestation, sex, ethnicity; duration of breastfeeding and current feeding; maternal paracetamol use whilst breastfeeding; current weight and length; family history of asthma and

allergies; history of wheezing, eczema and food allergies in the first months of life; lower respiratory tract infection; admissions to hospital; use of paracetamol or ibuprofen prior to index admission as well as paracetamol use with index admission; physical examination for the presence of eczema; feeding; illness including hospital admissions; use of other medications.

Phone follow-up data collection will be: Feeding; illness, including admission to hospital; wheeze questionnaire; use of study medication; use of other medications.

Home visit at 18 months data collection will be: Feeding; illness, including admission to hospital; use of study medication; use of other medications, questionnaire about wheeze, assessment of eczema; growth data taken from the parental held well child book (Tamariki Ora, often referred to as the Plunket book).

The final assessment at three years of age will be as for 18 months but include skin testing

Statistical analysis
The main outcome variable will be analysed by calculating the relative risk, expressed as an odds ratio, for the ISAAC study wheeze question, with adjustments for centre. Secondary analyses will adjust for the possible confounding variables outlines above. The secondary outcome variables of presence of atopy and eczema will be analysed in the same way.

Sample Size.
If the best recruitment domain is found to be infants admitted to hospital with RSV bronchiolitis:

- The prevalence of wheeze at age 3 after an admission to hospital with RSV bronchiolitis is 40%.[25] To detect a 20% reduction to 32% (relative risk 0.8) with 80% power and a type I error rate of 5%, we need to randomise a total of 1028 participants; for a 25% reduction to 30%, 712 participants.

If the best recruitment domain is found to be one of the domains in this pilot study, the sample size for the main proposed study will be calculated using the data collected in the pilot study.