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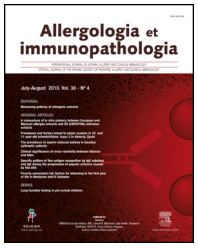

POINT OF VIEW

Asthma and paracetamol: Could we really know what happens between them?

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Abstract An association between paracetamol use or exposure in different times of life, including gestation and childhood, and asthma has been observed in recent years. Causality cannot be established from observational studies because of the arguable presence of many confounding factors and biases. Randomised trials are needed to disclose the nature of the association, but are difficult to carry out because of ethic, economic and logistical issues as large patient samples should be involved for a long time in such studies. Pragmatic trials may be the best option to shed some light on this issue. Questions regarding the problems and difficulties of conducting such trials and the way to overcome them are discussed.

Introduction

Asthma is a syndrome possibly including several conditions with different and not fully understood aetiopathogenic mechanisms. Since the identification of asthma depends on presence of symptoms, it is difficult to know when the disease begins and what factors are involved in its development. Associations with environmental factors such as air pollution, tobacco smoke exposure, diet, infections and medications have been identified. Some of them can intervene in very early stages of life such as the intrauterine period or early infancy. Paracetamol exposure is one of the factors that have been related to asthma development. The aim of this article is to review the published literature about paracetamol and asthma and analyse the studies that would be needed to undertake in order to clarify whether this association is causal or not.

Available information

Varner et al. were the first authors who proposed that the rising prevalence of asthma observed from the early 1980s

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could be related with the declining use of aspirin in favour of paracetamol.[1] Since then many articles have been published relating paracetamol consumption and asthma. This association has been studied in different populations and age groups including the wide range of observational studies: cross-sectional, ecological, case-control and cohorts.

Shaheen et al. published the first paper relating paracetamol exposure and asthma morbidity. In a population-based case-control study in adults they observed a dose-response relationship between paracetamol consumption, and asthma and rhinitis morbidity.[2] The same authors also observed this association in two international studies: the European Community Respiratory Health Survey (ECRHS), in adults, and the International Study of Asthma and Allergies in Childhood (ISAAC) in children.[3] Both studies showed that countries with a greater use of paracetamol had a higher prevalence of asthma, rhinitis and eczema; however this association was not significant when English-speaking countries were excluded. An association between paracetamol ingestion during pregnancy and increased risk of wheezing in the offspring was also found.[4]

Further studies reported this relationship between prenatal exposure to paracetamol and wheezing and asthma in infancy, although many bias and potential confounding factors may be involved.[5–7] In this regard, the study published by Kang et al., did not confirm that association after controlling for most of these factors.[8] Several other reviews have shown a positive association between use of paracetamol in pregnancy and asthma in the offspring although they stated that a causal relationship cannot be established until well-designed controlled studies are conducted.[9,10]

In an analysis of the large sample of children and adolescents included in the ISAAC study, Beasley et al. observed a dose-response relationship between paracetamol ingestion and symptoms of asthma, rhinitis and eczema.[11,12] Several cohort studies have confirmed this association between postnatal paracetamol ingestion and asthma,[13,14] but other studies adjusted for potential confounders such as the frequency of infections failed to show an association.[15]

Only one randomised double-blind clinical trial has been published comparing the short-term safety of paracetamol use versus ibuprofen in children with asthma.[16] In a secondary analysis of the data of this study, the use of ibuprofen appeared to reduce asthma morbidity over the short term compared with children taking paracetamol.[17] One review concluded that current use of ibuprofen was associated with the same or less risk to develop asthma symptoms when comparing to paracetamol.[18]

In recent years many exhaustive reviews and meta-analyses have been published examining the epidemiological evidence, the plausible pathogenic mechanisms, the causal relationship and the potential sources of biases of the association between paracetamol and asthma.[19–21] These reviews conclude that there is evidence of an association, regardless of the type of study, the age or time at exposure. Most of the studies find a dose-response relationship. Regarding the association between paracetamol and rhinitis, eczema or allergen sensitisation the evidence is much less clear. All the reviews conclude that there is a need for randomised controlled trials to establish the nature of the mentioned association.

Causal relationship and limitations of observational studies

Published studies show an evident association between paracetamol consumption and asthma. However, the key issue is whether a causal relationship exists, i.e. whether paracetamol exposure or ingestion is a risk factor for asthma. Maybe asthmatic children are more prone to infections or more symptomatic (fever) during infections than children without asthma. If that were the case, the greater use of paracetamol would be the consequence rather than the cause of suffering from asthma. As a matter of fact, antibiotic consumption in infancy has been linked to asthma and this association could be affected by the same bias suggested for paracetamol.[22,23]

Even if a causal relationship could be established, some questions arise. Does paracetamol exposure favour the inception, maintenance or worsening of asthma? Does it produce the same effect in the whole population or act differently according to the presence or absence of risk factors for asthma development (family history of asthma or atopy, for instance)? Does paracetamol act independently or in association with other factors? Would the effect be different depending on the timing of paracetamol exposure (pregnancy, childhood or adult life)? Observational studies do not allow answering these questions.

The need for clinical trials: conditions and limitations

To establish a causal relationship between paracetamol exposure and asthma, adequately designed clinical trials, preferable multicentre, with a large sample size and long term follow-up are needed. However, such trials face important obstacles, making them difficult or impossible to undertake. First, safety concerns about interventions in such early stages of human development as pregnancy and infancy raise ethical dilemmas and may be difficult to accept by Clinical Research Ethic Committees. Yet, paracetamol is authorised and is used in clinical practice without restrictions concerning age, pregnancy or breastfeeding. Secondly, the need to have a control group, who would be treated with placebo in case of fever or pain. If the drug is accepted to be effective against these symptoms, it would not be ethical to deprive patients of such symptom relief and therefore a trial vs. placebo would not be acceptable. One option would be to compare paracetamol versus an alternative drug, such as ibuprofen. That would not answer the question whether paracetamol induces asthma but rather whether another analgesic-antipyretic agent has the same or different effect about subsequent risk of asthma. And in practice, this is the answer the clinician and society need since it is not possible to completely avoid these drugs. Ibuprofen is similar in many ways, although not identical, to paracetamol. Its use is not well established in infants under three months and pregnant women and is contraindicated in the last trimester of gestation. Regarding safety and analgesic efficacy between paracetamol and ibuprofen, differences are minimal and, in practice, negligible.[24,25] A third problem emerges from the need of a double blinding design to avoid bias due to subjective perceptions from patient

and observer. These demands are not easy to fulfil as the drug has to be dispensed in a way that identification would be impossible when handling or ingesting it. Such blinding requires production and packaging of medications in sufficient amount to guarantee supply to all subjects included in the study and to design logistics to ensure correct distribution. On the other hand, blind administration of paracetamol and ibuprofen faces problems related to possible adverse events or wrong or accidental ingestion. That would force to have a permanent access to investigators in order to unblind the drug assigned to that subject and establish individual best treatment in each case.

In recent years, pragmatic trials are becoming widespread.[26] These are defined as studies comparing two or more interventions (two drugs, for instance), assigned on a random basis but administered in open-label mode under conditions of routine, everyday clinical practice. Pragmatic trials face some limitations but also provide advantages which make them preferable when double-blind clinical trials are not possible or are difficult to undertake. To establish effectiveness and safety of an intervention performed in conditions of clinical practice, recruitment of a large number of individuals, correct compliance of treatment and avoiding patients' dropouts are needed. If these requirements are not fulfilled, studied interventions lose potency and differences between groups tend to fade. Results of these studies are more reliable when concordant findings between subjective and objective variables are obtained. On the other hand, the results may not be extrapolatable to different populations. Despite its limitations, a pragmatic trial may be the best option to test whether a reduction of the risk of asthma in our little patients can be accomplished using one or another analgesic- antipyretic drug, or if this choice is irrelevant.

Another important factor to consider when it comes to designing a trial of this kind refers to the magnitude of the benefit obtained with the intervention and which can be considered clinically relevant. Since asthma is very prevalent in childhood, any reduction in the percentage of affected individuals may have important public health implications and cost savings. This reduction moreover may be present in the first years of life thus reducing short-term morbidity, or operate or persist in later years. As a consequence, the design of such a trial should include an adequate sample size to determine the magnitude of the benefit and its duration over time, taking into account the high risk of patients' dropouts typically occurring in trials of this type.

Conclusions

Possibly the best option to answer the questions raised in this article would be to conduct a multicentre pragmatic study comparing the incidence and prevalence of asthma in a cohort of children recruited during pregnancy or from birth, and randomised to treatment with paracetamol or ibuprofen when necessary. Over subsequent follow-up, drug ingestion, signs and symptoms of asthma, as well as the presence of allergen sensitisation and lung function would be recorded. An analysis of the collected information would allow to know the frequency of asthma in both groups, on an intention-to-treat basis and on actual compliance with the treatment. However, the difficulties of a study of this magnitude (referring to the number of patients, the duration of the intervention and follow-up, and the associated costs) make it difficult to undertake, despite the public health implications that its results would have. Will anyone be able to conduct such a work?

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