

**A BRIEF REVIEW ON - PARACETAMOL USE IN INFANCY IS LINKED TO
INCREASED RISK OF ASTHMA IN TEENAGERS****Dr. S. Naga Subrahmanyam^{1*}, Dr. D. Tagoore Vijaya Lakshmi², Dr. G. V. Pavan Kumar³ and Dr. G. V. Naga Raju⁴**¹M.Pharm.Pharm D, Assistant Professor, Department of Pharmacy Practice, Koringa College of Pharmacy, Korangi - 533461, Kakinda, A.P, India.²Department of Pharmacy Practice, Chalapathi Institute of Pharmaceutical Sciences, Guntur - 522004, A.P, India.³Associate Professor, Department of Pharmaceutical Chemistry, Koringa College of Pharmacy, Korangi - 533461, Kakinda, A.P, India.⁴Assistant Professor, Department of Pharmacy Practice, Koringa College of Pharmacy, Korangi - 533461, Kakinda, A.P, India.***Corresponding Author: Dr. S. Naga Subrahmanyam**

M.Pharm.Pharm D, Assistant Professor, Department of Pharmacy Practice, Koringa College of Pharmacy, Korangi - 533461, Kakinda, A.P, India.

Article Received on 12/09/2018

Article Revised on 03/10/2018

Article Accepted on 24/10/2018

ABSTRACT

Paracetamol, also known as acetaminophen or APAP, is a medicine used to treat pain and fever. It is typically used for mild to moderate pain relief. Evidence for its use to relieve fever in children is mixed. It is often sold in combination with other medications, such as in many cold medications. Paracetamol is available as tablets or capsules, liquid – usually for children soluble tablets (tablets that dissolve in water to make a drink), suppositories (capsules inserted into the back passage), an injection given into a vein – normally only used in hospital. The children had been recruited to the study before they were born because they were considered to be potentially at high risk of developing an allergy-related disease. They had at least one family member (mother, father or sibling) with a self-reported allergic disease (asthma, eczema, hay fever or a severe food allergy). After their birth, a research nurse rang the family every four weeks for the first 15 months, and then at 18 months and at two years old to ask how many days in the previous weeks had the child taken paracetamol. When the children were 18 years old, they gave a blood or saliva sample, which was tested for variants of the GST genes: GSTT1, GSTM1 and GSTP1. They were also assessed for asthma, and a spirometry test was performed to measure the amount of air inhaled and exhaled when breathing through a mouthpiece. One variant of the GSTP1 gene, GSTP1 Ile/Ile (in which the amino acid Isoleucine (Ile) is inherited from both parents), was associated with a higher risk of developing asthma. "We found that children with the GSTP1 Ile/Ile variant had 1.8 times higher risk of developing asthma by the age of 18 years for each doubling of the days of paracetamol exposure when compared to children who were less exposed," said Ms Dai. "In contrast, increasing paracetamol exposure in children who had other types of GSTP1 did not alter the risk of asthma. Our findings provide more evidence that paracetamol use in infancy may have an adverse effect on respiratory health for children with particular genetic profiles and could be a possible cause of asthma. However, these findings would need to be confirmed by other studies and the degree of adverse effect better understood before this evidence could be used to influence practice and before guidelines on paracetamol use are altered.

KEYWORDS: Paracetamol, acetaminophen, spirometry.**INTRODUCTION****Paracetamol**

Most people can take paracetamol safely, including pregnant women, breastfeeding women, children over 2 months of age – lower doses are recommended for young children. Always get advice before taking paracetamol if you have liver or kidney problems, have problems with alcohol, such as long-term alcohol misuse, underweight, taking other medications. Don't take paracetamol if you've had an allergic reaction to it in the past. Dose of paracetamol depends upon age, your weight, the type of paracetamol form and strength. For example: Adults can

usually take 1 or 2 500mg tablets every 4 to 6 hours, but shouldn't take more than 4g (8 500mg tablets) in the space of 24 hours. Children under 16 need to take a lower dose, depending on their age or weight – check the packet or leaflet, or ask a pharmacist or doctor for advice. For very young children, paracetamol liquid is given using a measuring spoon or an oral syringe. Paracetamol should start to work within an hour and the effect usually lasts several hours. Don't take more than the recommended dose if it isn't relieving your symptoms. Side effects from paracetamol are rare, but can include an allergic reaction, which can cause a rash

and swelling, flushing, low blood pressure and a fast heartbeat – this can sometimes happen when paracetamol is given in hospital into a vein in your arm blood disorders, such as thrombocytopenia (low number of platelet cells) and leukopenia (low number of white blood cells), liver and kidney damage if the dose exceeds (overdose) – this can be fatal in severe cases.

Asthma

Asthma is an inflammatory disease of the airways to the lungs. It makes breathing difficult and can make some physical activities difficult or even impossible. According to the Centers for Disease Control and Prevention (CDC), approximately 27 million Americans have asthma. It's the most common chronic condition among American children: 1 child out of every 12 has asthma.

Epidemiology

Evidence is accumulating that the use of acetaminophen may increase the risk of developing asthma and that its widespread increasing use over the last 30 years may have contributed to the increasing prevalence of asthma in different countries worldwide.^[1,2] The evidence is based primarily on epidemiological studies, which have reported that exposure to acetaminophen in the intrauterine environment,^[3-7] childhood,^[6,8,9] and adult life^[10-13] is associated with an increased risk of asthma, together with one randomized controlled trial reporting increased rates of hospital visits for asthma in children taking acetaminophen compared with ibuprofen.^[14] The potential mechanisms for these effects of acetaminophen include oxidant-induced airway inflammation and enhanced Th2 responses.

Symptoms of severe asthma were defined by the responses to the following written questions

1. "How many attacks of wheezing have you had in the past 12 months"? None/1 to 3/4 to 12/More than 12. Participants who reported four or more attacks were considered to have symptoms of severe asthma.
2. "In the past 12 months how often, on average, has your sleep been disturbed due to wheezing?" Never woken with wheezing/Less than one night per week/One or more nights per week. A response of one or more nights per week was considered to indicate symptoms of severe asthma.
3. "In the past 12 months, has the wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?" Yes/No. A positive response was considered to indicate symptoms of severe asthma

Children who are prone to occurrence of asthma

Children who take paracetamol during their first two years of life may be at a higher risk of developing asthma by the age of 18, especially if they have a particular genetic makeup, according to new research presented at the European Respiratory Society International Congress.^[16]

Ms Xin (Daisy) Dai told in the meeting that the link between paracetamol use and asthma seemed strongest in those who had a particular variant of the glutathione S-transferase (GST) gene, GSTP1. However, she warned that the research showed only that there was an association between paracetamol and asthma, not that paracetamol caused the condition; further research was needed to confirm her findings and fully understand the link. She also found that another GST gene variant, GSTM1, was linked with reduced lung function.

Cause for Asthma in children

GST genes contain the instructions for making enzymes that use an antioxidant called glutathione to mop up the effects of exposure to toxins in the body and the lungs. This mechanism helps to prevent damage to cells and inflammation. "Paracetamol, on the other hand, consumes glutathione, reducing the body's capacity to deal with toxic exposure," explained Ms Dai. "We hypothesized that people who did not have full GST enzyme activity because of common genetic variations or deletions may be more susceptible to adverse effects on the lungs from paracetamol use."

Investigation and analysis

s Dai, who is a nurse and PhD candidate at the Allergy and Lung Health Unit at the University of Melbourne, Australia, and her colleagues investigated their hypothesis in 620 children who had been followed from birth to 18 years old as part of the Melbourne Atopy Cohort Study. The children had been recruited to the study before they were born because they were considered to be potentially at high risk of developing an allergy-related disease. They had at least one family member (mother, father or sibling) with a self-reported allergic disease (asthma, eczema, hay fever or a severe food allergy).

After their birth, a research nurse rang the family every four weeks for the first 15 months, and then at 18 months and at two years old to ask how many days in the previous weeks had the child taken paracetamol. When the children were 18 years old, they gave a blood or saliva sample, which was tested for variants of the GST genes: GSTT1, GSTM1 and GSTP1. They were also assessed for asthma, and a spirometry test was performed to measure the amount of air inhaled and exhaled when breathing through a mouthpiece.

One variant of the GSTP1 gene, GSTP1 Ile/Ile (in which the amino acid Isoleucine (Ile) is inherited from both parents), was associated with a higher risk of developing asthma.

"We found that children with the GSTP1 Ile/Ile variant had 1.8 times higher risk of developing asthma by the age of 18 years for each doubling of the days of paracetamol exposure when compared to children who were less exposed," said Ms Dai. "In contrast, increasing

paracetamol exposure in children who had other types of GSTP1 did not alter the risk of asthma.

"We also found effects in children who had a variant of GSTM1 in which one part is not functioning. In these children increasing paracetamol use was associated with small, but significant reduction in the amount of air they could forcibly breathe out in one second at 18 years. It is not known if the relationship we found between paracetamol use and lung function is clinically important. In addition, we found some weak evidence that paracetamol use in the first two years of life may be associated with reduced lung function in adolescence regardless of which variants of the GST genes the children had."

CONCLUSION

Our findings provide more evidence that paracetamol use in infancy may have an adverse effect on respiratory health for children with particular genetic profiles and could be a possible cause of asthma. However, these findings would need to be confirmed by other studies and the degree of adverse effect better understood before this evidence could be used to influence practice and before guidelines on paracetamol use are altered.

"There is mounting evidence that the GST superfamily of genes, including three major classes -GSTM1, GSTT1 and GSTP1 - are associated with various diseases, including cancers, asthma, atherosclerosis, allergies, Alzheimer's and Parkinson's disease. Our study adds to this body of evidence."

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