Should Children with Sickle Cell Disease and Asthma be using Paracetamol for Pain Relief?

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ABSTRACT
Sickle cell Disease (SCD) is a genetic disorder that causes the production of abnormal red cells. This chronic disease leads to many complications such as vaso-occlusion in the lungs and blood vessels. This often leads to great pain and often paracetamol is used. However, there has been increasing significant evidence that the use of paracetamol in early life and in gestation causes an increased risk in the development of asthma in the child. Additionally, there has been evidence to show that another possible complication of SCD is the development of asthma due to the disruption of the nitric oxide (NO) pathway and increase leukotriene in SCD. This further increases the morbidity of SCD patients. This essay will thus discuss whether paracetamol should be used in children with SCD and asthma.

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INTRODUCTION
Sickle cell Disease (SCD) is a genetic disorder where the body produces abnormally shaped red blood cells, which leads to anaemia. The sickle mutation results in a substitution of glutamic acid to valine in the 6th amino acid position of the β-globin protein, leading to the production of haemoglobin S (HbS). SCD is an autosomal recessive condition, hence when the mutation is inherited in heterozygosity, it causes no clinical significance and individuals are referred to as ‘carriers’. When inherited in homozygosity or if individuals are compound heterozygous with another relevant mutation in the β-globin gene, a clinical syndrome of SCD occurs. As valine is a hydrophobic amino acid, whilst glutamic acid is hydrophilic, this causes a change in the physical property of the haemoglobin molecule. In low oxygen saturation, HbS will aggregate to form rods or crystal-like polymers (Figure 1), causing the red cells to become sickle-shaped. These ‘sickle’ or crescent-shaped cells may aggregate and cause a blockage in blood vessels (vaso-occlusion) (Ware et al., 2017). Vaso-occlusion leads to tissue hypoperfusion and subsequent reperfusion, leading to pain.

The polymerisation of HbS leads to extravascular haemolysis and reduction in red cell lifespan (approximately 10-20 days instead of 120 days) (Simon, 2013). This results in chronic anaemia and high turnover of erythropoiesis.

It is estimated that 250,000 of the population are born with SCD each year (Lervolino et al., 2011), and it is mostly seen in African and other malaria endemic regions. HbS mutation in heterozygosity provides a degree of malarial protection and this has resulted in its positive selection through human evolution, leading to several malarial-endemic regions to have as much as 40% carrier rates. (Ashley-Koch, Yang and Olney, 2000). In the UK, it is mostly seen in individuals from African or Caribbean background (NHS, 2016).

In children with SCD, symptoms do not usually arise immediately after birth. Affected infants may develop SCD-related complications after 5-6 months of age as the production of the protective fetal haemoglobin (HbF) is switched off, making way to the production of HbS as the predominant haemoglobin type, leading to sickling. Symptoms of SCD include: fatigue due
to the anaemia, severe debilitating widespread episodic pain, susceptibility to infection with encapsulated bacteria, acute chest syndrome, nocturnal enuresis, exercise intolerance, etc. (Oni et al., 2013).

Although treatment for SCD with curative intent, such as bone marrow transplantation, has been available for several decades, its cost and toxicities preclude its widespread use. Hence treatment is mainly focused on symptom alleviation and prevention of chronic organ damage. Simple supportive measures such as avoidance of exposure to cold and windy environmental conditions, dehydration and preventable infections help with minimising vaso-occlusive episodes (Oni et al., 2013). Hydroxyurea, an antimitabolite that targets the cell cycle in the S-phase is frequently given for the prevention of vaso-occlusion. Pain relief is frequently obtained by simple analgesia with paracetamol and non-steroidal anti-inflammatory agents such as ibuprofen (Blake and Lima, 2011). Sepsis related morbidity and mortality are reduced by prophylactic antibiotics. This is also achieved through additional vaccinations against encapsulated bacteria and influenza virus and prompt and effective management of acute septic episodes with broad-spectrum anti-microbials (Ballas, 2002). Red cell transfusions are also used (Oni et al., 2013).

![Pathophysiology of SCD](image-url)

**Figure 1 - Pathophysiology of SCD.** In a low oxygen condition, deoxyHbS will aggregate. Mutation in the 6th position, which causes the change of protein from glutamic acid to valine, causes the change in the properties of the Hb chain. This aggregation causes the vaso-occlusion in the circulation and haemolytic anaemia, which is associated in a sickle cell crisis (Image taken from Odievre et al., 2011).

Children with sickle cell disease are able to live a normal life. However, some children may develop strokes, serious infections and lung issues, which may lead to death (Platt et al., 1994). Life expectancy in SCD is low, with a median survival of 60 years and a median age at death of 40 years in high-income countries. There is significant phenotypic variation in SCD and a number of environmental and genetic factors are implicated in the variability (Oni et al., 2013).

Children with SCD also have co-morbidities that may affect their prognosis. One of these is asthma.

**ASTHMA**

Asthma is a chronic lung condition due to the inflammation of bronchi and narrowing of the airways. The narrowing of the airway can be induced by allergens, irritants (e.g. smoke/ cold air), exercise, and respiratory infections. The
presentation can vary between patients especially in children (Murphy et al., 2015).

In general, there are 2 asthmatic responses: immediate and late. An immediate asthmatic response occurs as a result of an allergic reaction leading to the release of immunoglobulin E (IgE) that in turn triggers an inflammatory process, causing degranulation of mast cells and release of histamine. This is sometimes followed by a late response for a longer period of time. This response is due to antigen presenting cells being recognised by CD4 T-helper (subclass 2) cells, which causes the release of cytokines and interleukins causing further IgE molecules to be released. This leads to mucus hyper-secretion and remodelling of the airway (Fehrenbach, Wagner and Wegmann, 2017), increases in the thickness of reticular basement membrane (RBM) and smooth muscle of airways (Jeffery, 2011) (Figure 2).

![Pathophysiology of asthma](http://hubpages.com/health/Pathophysiology-of-Bronchial-Asthma)

**Figure 2** - Pathophysiology of asthma. The environmental trigger causes the release of IgE to stimulate an inflammatory response that leads to short-term inflammation as well as long-term remodelling of the airways and mucus hypersecretion. This causes bronchospasm, acute inflammation, persistent inflammation and remodelling on the airways. In the short term (left-side) / acute inflammation triggers the inflammatory response. In the long term, (right-side) from persistent inflammation and development remodelling, it causes a change in the microenvironment of the airways. (Image modified from http://hubpages.com/health/Pathophysiology-of-Bronchial-Asthma)

The prevalence of asthma within the general population has increased in recent years. Based on The 2014 Global Asthma Report, as many as 14% children have experienced asthma symptoms (Ait-Khaled et al., 2014). It is the most common chronic inflammatory disease in children (World Health Organisation, 2013) and can be fatal if not treated properly, therefore protocols and regular checks are required (Bush and Fleming, 2015).

The symptoms of asthma are wheezing, breathlessness, tight chest and coughing (NHS, 2016).

There is some controversy about the use of steroids for asthma treatment in limiting children’s growth and the combination of drugs used (Morris and Mellis, 2001). However, in general asthma treatment is classified into 2 categories: relievers and preventers. The relievers
that are used are bronchodilators such as beta2 adrenoreceptors agonists (e.g. salbutamol), anticholinergics / muscarinic receptor antagonist (e.g. ipratropium), and xanthines/ phosphodiesterase inhibitors (e.g. theophylline). Meanwhile preventers are steroids (e.g. glucocorticosteroid), and antileukotrienes (e.g. montelukast), most of which are targeted to reduce the inflammatory effect of the hypersensitive cells (Barnes, 2012).

Some symptoms of asthma, such as wheezing are relatively common in children (especially in preschool children) however, only half of those go on to develop childhood asthma. In these children, early airway remodelling is seen and this is a good indication for further asthma advancement (O’Reilly et al., 2013).

In children with SCD however, asthma is more commonly seen (approximately 25%) (McClain et al., 2016). Some correlation has been made between asthma and SCD in children. This correlation is thought to be due to the Nitric Oxide pathway. The level of L-arginine (precursor of NO) is reduced in sickle cell. Its reduction causes the epithelium to be more prone to damage and hyperactivity of the airways, which increases the probability of the development of asthma (Blake, K. and Lima, J., 2011).

Asthma in SCD patients can potentially complicate treatment (e.g. opioids that are used in a sickle cell crisis need to be used carefully on children with an asthma co-morbidity) (Ballas, S., 2002). Although the specific relationship is not fully understood, asthma is also thought to increase the risk of acute chest syndrome in SCD children. Hence, it reduces the quality of life and life expectancy of patients (Blake, K. and Lima, J., 2011).

In dealing with episodes of sickle cell crisis, paracetamol is often used as a painkiller before opioids are considered.

**PARACETAMOL**

Paracetamol is a mild analgesic drug. The chemical structure of paracetamol is seen in (figure 3). It consists of a phenol group and a peptide bond (Graham et al., 2013). It has a biological half-life of 1-3 hours. Paracetamol is mostly metabolised in the liver and excreted in the urine (Forrest, Clements and Prescott, 1982)

![Chemical structure of Paracetamol](image)

*Figure 3 - Chemical structure of Paracetamol. It consists of a phenol group and a peptide bond. Image taken from chemistry.about.com*

It has an anti-pyretic, and analgesic property. Although not understood fully, it is thought that paracetamol inhibits prostaglandin production. It inhibits cyclooxygenase (COX) and has a high specificity for COX-2 (figure 4) (Dills, Anderson and Pierce, 2012). Peripherally it acts on the nociceptors by prostanoids reducing sensation (Ballas, 2002). In addition, it also has the property of being an antipyretic, making paracetamol a common drug used to reduce fever (Beasley et al., 2008), as it is able to result in the hypothalamus reducing the increase in body temperature that is due to prostaglandins (Aronoff and Neilson, 2001).
Figure 4 - COX Pathway. Phospholipids are broken down to Arachidonic acid, which will be broken down to Prostaglandin, Prostacyclin, Thromboxanes and Leukotrienes. Paracetamol and other COX-2 inhibitors (or NSAIDS) will inhibit the formation of Prostaglandin (acts on smooth muscles), Prostacyclin (acts on endothelium) and Thromboxane (acting on platelets). Image taken from Medscape.com.

The use of paracetamol, although common, has its controversies. There is some research that indicates that the use of paracetamol in intrauterine life or early infant life might increase the risk of asthma development in children (Farquhar et al., 2009). This might prove problematic especially for children with SCD who use paracetamol in early-life and already have a high risk of asthma due to the SCD itself.

This essay will discuss the role that paracetamol takes in the treatment and management of asthma and SCD in children; the advantages and disadvantages of using paracetamol, and whether paracetamol should really be used in the treatment of children with SCD and asthma.

PAIN IN SCD

Pain is the most predominant symptom in SCD and is the commonest cause for hospital admissions. Pain occurs as a result of a vaso-occlusive episode (VOE) leading to ischaemia-reperfusion and the release of nociceptive stimuli. Acute chest syndrome (ACS), another common and significant complication, can also present with pain. ACS is defined as “a new pulmonary infiltrate involving at least one complete lung segment that is consistent with the presence of alveolar consolidation, but excluding atelectasis” (Vichinsky et al., 2000) and presenting with chest pain, fever, wheezing or cough (Ware et al., 2017).

The pain in ACS and VOE is mostly due to the occlusion of blood flow leading to tissue ischaemia. This tissue injury will activate A-delta fibres that detect thermal and mechanical stimuli as nociceptive. The stimulus will undergo transduction from mechanical to an electrical stimulus and be transmitted to the 1st order nociceptive neuron. It will then be transmitted to the central nervous system at the dorsal horn level and become the 2nd order sensory neuron. It does not project axon collaterals into the dorsal column but will have short collaterals, which synapse exclusively within the ipsilateral dorsal horn. It will then immediately synapse on the dorsal horn of the spinal cord on the projection neuron present.
on lamina that consists of nociception-specific neurons and lamina 5 that is for innocuous, nociceptive and wide dynamic neurons. From lamina 1 it mostly enters the spinothalamic pathway to the thalamus, meanwhile from lamina 5 the impulse goes to the brainstem and thalamus (Kandel and Mack, 2012).

Perception of the nociceptive stimuli activates the projection neuron of the ascending pathway through the spinothalamic, spinoparabrahcial and spinoreticular pathways. It can be sent directly to the cortex, or indirectly to the brain stem. Most pathways will run in the contralateral spinal cord (except for the spinoreticular tract) and most will be in the anteroventral position. The pathways will terminate in a variety of areas of the brain. The spinothalamic pathway is mainly responsible for carrying localised information (sensory and discriminative) whilst the others are linked to cognitive, affective, motivational components of pain. Overall, this will inform the brain where the damage is. Projection to the ventral posterior nucleus of the thalamus gives input to the somatosensory cortex about localisable pain and lesions. Projection to a variety of subcortical structures allows arousal, modulation and reticular formation projection to the medial nucleus. Meanwhile, projection to the medial nucleus of the thalamus (to the insular cortex) allows differentiation to attribute specific function to detect the lesion and allow the ability to feel and distinguish the pain, so as to respond in an appropriate manner (Kandel and Mack, 2012).

This is difficult to pin-point exactly where pain perception occurs, however major regions that are active would be the primary and secondary somato-sensory, anterior cingulate, insular and prefrontal cortex and the thalamus. From here, modulation of the pain occurs. The most commonly known theory to explain this is the gate control theory. Small interneurons in the dorsal horn act as a gate that controls the amount of excitation of transmission. There are a few factors that regulate the gate, such as the amount of activity in nociceptive fibres (e.g. in this case the fibres in the ischaemic tissues), the amount of activity in other peripheral fibres, messages descending from the brain. The stimulation of certain areas of the brain stem (such as the periaqueductual grey) can induce analgesia (McMahon, 2013) (Kandel and Mack, 2012).

**ASTHMA AND SCD**

Asthma is an increasingly common chronic disease in children. However, it is even more common in children with SCD. It is thought that 25% of SCD children have asthma, excluding those undiagnosed (McClain et al., 2016). Asthma in SCD is defined “clinically by a physician diagnosis, an acute asthma exacerbation, or use of asthma medication” (Shilo and Lands, 2011). SCD children with asthma usually present with wheezing, shortness of breath, have a family history of asthma, and a positive skin prick allergy test (DeBaun and Strunk, 2016).

Asthma is one of the risk factors that increase the mortality and morbidity in SCD. This is because ACS is commonly due to the hypoxia in the lungs that can be triggered by an infection or an embolus. In this situation, the airways in the lungs are already narrow and similar to asthma and an inflammatory response is triggered in response. A seemingly innocuous respiratory infection can cause complications in SCD patients. In the presence of asthma, it further triggers the inflammatory mediators and reactive oxidants that increases the adhesion molecules causing an increase in aggregation of red blood cells in both, the lungs worsening the ACS, and in the body, triggering a vaso-occlusive Crisis (VOC) (Shilo and Lands, 2011).

It is also the thought that SCD causes a chronic pro-inflammatory state that is characterised by an increase in white blood cells and adhesion molecules in a mice-model study done by Holtzelaw et al. (2004). This study suggests that any further inflammatory triggers may cause decompensation, such as bronchial obstruction. The inflammatory response leads to long-term damage due to its additive effect, as lungs in SCD patients are already in a more inflamed state, and there is increased risk of pulmonary hypertension due to injury to the endothelium. Therefore, the presence of asthma, which is due to hypersensitivity, makes the lungs even more sensitive, possibly causing an increase in ACS episodes and other lung complications that reduce the lung’s capability.

The incidence of asthma in ACS in itself has been strongly correlated. Studies have shown that a confirmatory diagnosis of asthma increases the occurrence of ACS episodes and the severity of pain in an ACS. This is especially for patients that have had a history of ACS. Additionally, the presence of asthma is correlated with an increase in mortality rate (DeBaun and Strunk, 2016).
Although the definite correlation is unknown, there are a few possible theories that suggest the risk of the development of asthma in SCD patients. The first possible link might be due to the nitric oxide pathway (figure 5). In SCD, NO availability is decreased due to a few reasons. The first being the breakdown of red blood cells forms free plasma haemoglobin that consumes NO and produces free radicals that further take-up NO. Secondly, there is a decrease in NO formation due to the reduction in plasma arginine as erythropoiesis increases arginase plasma levels. This results in a competition with NO synthetase for arginine.

Figure 5 – The change in the formation and breakdown of arginine in SCD and the link to asthma. Arginine is produced from citrulline. Arginase and nitric oxide synthase (NOS) both use arginine as a substrate. In SCD, arginine and NO is reduced due to the breakdown of red blood cells. The release of red blood cell arginase during haemolysis increases arginase concentration in the plasma, which results in an increased production of ornithine (change in metabolism). This will reduce the amount of arginine for NO production. Arginine will also be further reduced due to an increase in ornithine that competes with arginine as both are transported in a similar way. Therefore, even though there is an increase in NOS, NO production is low due to a lack of substrate. The reduction in NO and an increase in ornithine most likely results in the damage of the lungs and asthma. Image taken from (Gomez and Morris, 2013)

Another possibility is through the role of leukotriene in the inflammatory pathway. SCD is an inflammatory state with an increase of cytokine (e.g. IFN-gamma, TNF-alpha, etc.) release. The release of cytokines increases in the presence of asthma too. Leukotriene plays a role in this, as they signal inflammation and bronchoconstriction. Arachidonic acid (AA) is formed from leukotriene (Gomez and Morris, 2013) (figure 6). AA is also from phospholipase A2 that is also known to
cause ACS and VOEs (Styles et al., 1996). AA forms 5-hydroperoxycosatetraenoic acid and LTA4 by 5-lipoxygenase (ALOX5), which will be converted to LTE4 (figure 2) (Kanaoka and Boyce, 2004) (Wood et al., 1999). LTE4 is most commonly higher in children with both SCD and asthma. The level of LTE4 is known to be a good indicator of the incidences of VOEs and the number of hospitalisations (Shilo and Lands, 2011).

Figure 6 - Biochemical pathway of Leukotriene. Enzymes are in blue, products in yellow, co-factors in green and drugs in red. Cysteine phospholipase A2 will be converted to Arachidonic Acid (AA). With 5-Lipoxygenase-activating protein and the enzyme 5-lipoxygenase (transcribed from the ALOX5 gene), AA will be converted to Leukotriene A4 (LTA4). LTA4 will then be converted to form Leukotriene B4 (LTB4) or Leukotriene C4 (LTC4) using the enzyme Epoxide hydrolase and Leukotriene C4 synthase respectively. In asthma, LTC4 plays a more major role than LTB4. LTC4 will be converted to Leukotriene D4 (LTD4) and Leukotriene E4 (LTE4), which will all act on the cysteiny1 leukotriene-1 receptor (CysLT1 receptor) on the surface of airway cells. These cytokines will initiate an inflammatory pathway leading to smooth-muscle constriction, eosinophil migration and oedema that are usually associated with asthma. Image taken from Wood et al. (1999).

Cysteine leukotrienes (LT) are inflammatory mediators and are products from AA by cytosolic phospholipase A2. Most asthma symptoms that are due to the release of certain LT (e.g. LTC4, LTD4 and LTE4) are through the activation of cysteiny1 leukotriene-1 and 2 receptors (CysLT1) (Wood et al., 1999) (figure 6). In SCD, the level of LTE4 is raised (Jennings et al., 2008) which is related to more pain and ACS episodes (Field et al., 2009). Therefore, the inflammatory pathway is behind both SCD and asthma and leukotrienes play a major factor in the formation of these disease.

Thirdly, there is also a genetic factor that contributes to the increased risk of asthma. The mutation in the promoter of the ALOX5 gene, which codes for enzymes that take part in the synthesis of cysteine leukotrienes, is affected in both asthma and SCD patients (In et al., 1997) (Kalayci et al., 2005). This mutation gives rise to a reduction in transcription. Additionally, the increase expression of 5-lipoxygenase and 5-
lipoxygenase activating protein increases in blood cells of SCD patients (Patel et al., 2008). This increase is due to an increase in placenta growth factor that is tied with SCD severity (Blake and Lima, 2011). Although the definite correlation between the mutation of this gene in asthma and SCD is unknown and needs to be further researched, it is thought to contribute to the pathophysiology of both these diseases.

Therefore, speculatively, the leukotriene pathways, especially the production of the Arachidonate 5-Lipoxygenase, take part in both the pathology of asthma and SCD and could provide the link to the increased risk of asthma in SCD patients. However, this requires further research.

Although the reason behind the correlation is unclear, it is certain that the presence of asthma in SCD reduces the quality of life of the patient. However, it is still seen to be difficult to diagnose asthma in SCD patients, due to the similar presentation of symptoms between asthma and an ACS (DeBaun and Strunk, 2016). The presentation of ACS of chest pain, wheezing or cough is very similar to the symptoms found in asthma. Meanwhile, the treatment strategies are different. For this reason, management of asthma in SCD patients is not very effective.

Research by Shilo and Lands, (2011) and McClain et al., (2016) suggest that there is a lack of coherent treatment plan for patients with asthma and SCD. It is recognisable that although similar, the pathophysiology of ACS and asthma is different. McClain et al. suggested, the implementation of an integrated care for patients with asthma and SCD with the presence of both a respiratory team and sickle cell team to manage an ACS with asthma. The result yielded a lower airway obstruction and better usage of an asthma action plan for the children resulting in a better quality of life. Although it is to be noted that the number of VOEs did not decrease (McClain et al., 2016).

In summary, there are a few possible speculations on how asthma develops in SCD patients from the NO pathway to the increase in leukotrienes causing inflammation. The development of asthma increases patients’ morbidity.

PARACETAMOL AND ASTHMA

One of the main forms of analgesia used in sickle cell management is paracetamol (Madadi et al., 2012). It is used in mild to severe cases of pain. The action of paracetamol is more speculative than experimental and is thought to act on the COX pathway as previously discussed.

Though paracetamol is definitely useful in pain management, the use of paracetamol can be debatable. There have been multiple studies that indicate the causative relationship between paracetamol and asthma. The use of paracetamol in early children’s life (foetal life or infant) increases the risk of the development of childhood asthma. In children with SCD, this might cause further problems as SCD patients already have an increased risk of asthma due to the similar pathophysiology, as mentioned above. With the increased administration of paracetamol (e.g. in instances as a first-line treatment for pain in sickle cell episodes), it further compounds the risk of the development of asthma.

The risk of asthma development is tied with the time of administration of paracetamol.

PARACETAMOL USE IN PREGNANCY

In the earliest form of its research, Shaheen conducted a study that paracetamol, in late pregnancy (20-32 weeks), increased the risk of wheezing in offspring at 30-42 months (3 years) (Odds ration (OR) = 2.1) (table 1). This could possibly be due to the fact that this is the critical embryonic period for the development of the respiratory system.

A study conducted in Denmark in 2008, reported similar results. The use of paracetamol, generally in pregnancy, led to persistent wheezing in the children and hospitalisation due to asthma at 18 months and a possible diagnosis of asthma at 7 years old (table 1). Similar results are seen in the study conducted in Spain in 2008, Sweden in 2011 and United States in 2015.

The emergence of persistent wheezing is very important, especially if it starts early in life and the child has a family history of asthma. Persistent wheezing is associated with an increase in IgE levels (P< 0.01) and a reduced Maximum Volume of Lung Functional Residual Capacity (VmaxFRC) (P<0.01) by the age of 6 (Young et al., 2000). Recurrent wheezing also results in a reduction in FEV1/FVC (Granell, Henderson and Sterne, 2016) indicating a reduction in lung function and possibly an increased risk of the development of an obstructive disease such as asthma.

In the study conducted by Sordillo et al., (2015), the use of paracetamol in pregnancy did
not seem to result in an increased hypersensitivity and allergy reaction in childhood. However, it did show a significant statistical result that it increases the incidence of recurrent wheezing by 53% and asthma by 36% when the children are followed up at age 3-5 years old. This is however the unadjusted data. A clear concern from this research was that after the incidences of respiratory infections have been accounted for, the risk seems to decrease to 41% and 26% respectively (Sordillo et al., 2015).

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Exposure in pregnancy</th>
<th>Comparison</th>
<th>Sample size (n)</th>
<th>Age of children</th>
<th>Outcome</th>
<th>Odd Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>2002</td>
<td>20-32 weeks</td>
<td>Most days/daily vs. no use</td>
<td>9400</td>
<td>3 years</td>
<td>Current wheezing</td>
<td>2.10 (1.30-3.41)</td>
</tr>
<tr>
<td>Denmark</td>
<td>2008</td>
<td>During pregnancy</td>
<td>Ever use vs. no use</td>
<td>56455</td>
<td>18 months</td>
<td>Wheezing</td>
<td>1.13 (1.07-1.175)</td>
</tr>
<tr>
<td>Spain</td>
<td>2008</td>
<td>During pregnancy</td>
<td>At least 1x/month vs. no use</td>
<td>1741</td>
<td>3-5 years</td>
<td>Current wheezing</td>
<td>1.71 (1.15 – 2.53)</td>
</tr>
<tr>
<td>Sweden</td>
<td>2011</td>
<td>During pregnancy</td>
<td>Ever use vs. no use</td>
<td>4496</td>
<td>4.5 years</td>
<td>Multiple wheeze</td>
<td>2 (1.1 – 3.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ICS* treated wheeze</td>
<td>1.8 (1.2.2.6)</td>
</tr>
<tr>
<td>United States</td>
<td>2015</td>
<td>During pregnancy</td>
<td>Ever use vs. no use</td>
<td>1490</td>
<td>3-5 years</td>
<td>Recurrent wheezing</td>
<td>1.53 (1.23-1.80) (unadjusted)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asthma</td>
<td>1.41 (1.06-1.89) (adjusted)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>1.36 (1.14-1.61) (unadjusted)</td>
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<td></td>
<td>1.26 (1.02-1.58) (adjusted)</td>
</tr>
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</table>

Table 1 – Table comparing the different research done on the relationship between uterine exposure to paracetamol and the risk of wheezing and development of asthma in childhood. Different time of exposure was also tested during pregnancy and the age at which the effect is measured also varies, however all the research points to the fact that the use of paracetamol in early fetal life increases the risk of wheezing. The adjustment made in the 2015 study by Sordillo et al. is for respiratory infections. Table modified from Farquhar et al., (2009).

*ICS = Inhaled Corticosteroid

**PARACETAMOL USE IN INFANCY.**

The exposure of paracetamol in early infant life has also been associated with an increase in wheezing and even a clinical diagnosis of asthma in the future. The most well-known research is the Phase 3 International Study of Asthma and Allergy in Children (ISAAC) in children. Out of the 205,487 children, the use of paracetamol in the first 12 months of life increases the risk of asthma-like symptoms by 46% (table 2).

Similar results were observed in the study in Australia in 2010, Italy in 2011 and United States in 2015. The study in Italy indicated a very strong relationship and evidence (OR= 1.77) (table 2) for the administration of paracetamol in the first year of infancy to the onset of persistent wheezing in the child later in life.
<table>
<thead>
<tr>
<th>Country</th>
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<th>Exposure in childhood</th>
<th>Comparison</th>
<th>Sample size (n)</th>
<th>Age of children</th>
<th>Outcome</th>
<th>Odds ratio (95% confidence interval)</th>
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</thead>
<tbody>
<tr>
<td>ISAAC III (Beasley et al., 2008)</td>
<td>2008</td>
<td>0-1 year</td>
<td>1/year or more r</td>
<td>205487</td>
<td>6-7 years</td>
<td>Asthma symptoms</td>
<td>1.46 (1.4-1.6) (multi-variate analysis)</td>
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<tr>
<td>Australia (Lowe et al., 2010)</td>
<td>2010</td>
<td>0-2 year</td>
<td>Ever use vs no use</td>
<td>295</td>
<td>6-7 years</td>
<td>Asthma</td>
<td>1.2 (1.0-1.4)</td>
</tr>
<tr>
<td>Italy (Rusconi et al., 2011)</td>
<td>2011</td>
<td>0-1 year</td>
<td>Ever use vs no use</td>
<td>16933</td>
<td>6-7 years</td>
<td>Persistent Wheezing</td>
<td>1.77 (1.49-2.1)</td>
</tr>
<tr>
<td>United States (Sordillo et al., 2015)</td>
<td>2015</td>
<td>0-1 year</td>
<td>Ever use vs no use</td>
<td>1490</td>
<td>3-5 years</td>
<td>Recurrent wheezing</td>
<td>1.29 (1.06-1.56) (unadjusted)</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>1.05 (0.85-1.31) (adjusted)</td>
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<td></td>
<td></td>
<td>1.21 (1.04-1.41) (unadjusted)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>1.03 (0.88-1.22) (adjusted)</td>
</tr>
</tbody>
</table>

Table 2 – Table comparing the different research done on the relationship between infant exposure to paracetamol and the risk of wheezing and development of asthma in childhood. Different time of exposure was also tested during childhood (mostly during the first year of child life) and the age at which the effect is measured also varies, however all the research points to the fact that the use of paracetamol in early infant life increases the risk of wheezing and the clinical diagnosis of asthma later on in life. In the ISAAC III, asthma symptoms are defined as wheezing. The adjustment made in the 2015 study by Sordillo et al. is for respiratory infections. Table modified from Henderson and Shaheen, 2013

*ICS = Inhaled Corticosteroid

In the study by Sordillo et al., (2015) it was observed that paracetamol in the 1st year of infant life results in recurrent wheezing (OR= 1.29) (table 2) and a diagnosis of asthma (OR= 1.21) by the age of 3-5 year old. However, after adjustment for respiratory infections, the association becomes statistically insignificant. This observation, in addition to the finding of the use of paracetamol in pregnancy from the same study, suggested that maybe the presence of respiratory infections (regardless of the administration of paracetamol) plays a certain role in the increase in wheezing and the exacerbation of asthma, instead of the direct effect of paracetamol itself (Sordillo et al., 2015).

Although there are many statistically significant data and strong evidence for the link of paracetamol and the increased risk of asthma, a lot of these studies acknowledge the presence of limitations that can possibly have an impact. The first would be the use of parental recall for data collection. This can ultimately be biased. In addition, as paracetamol is an over-the-counter drug, it is difficult to collect accurate data of the dosage taken. Therefore, these studies have limitations too.
POSSIBLE MECHANISMS

The definite mechanism of why paracetamol possibly increases the risk of asthma is still unknown. However there are a few suggested mechanisms that can potentially lead to it.

The main possible mechanism would be that paracetamol reduces macrophages in the lungs, type II pneumocytes and the release of TNF alpha and IL-6, and glutathione (GSH) resulting in the reduction in protection against respiratory antioxidant (Dimova et al., 2005). GSH levels are usually low in an asthma attack, but are usually seen after an attack. It is suggested to aid the recovery of cells that were damaged due to the free radicals. GSH is required to protect the epithelium from free radicals and other injuries due to oxygen (Brown, 1994). Free radicals lead to tissue damage (Freeman and Crapo, 1982), contraction in the smooth muscle (Rubanyi, 1988) (Rhoden and Barnes, 1989), inflammation (Dimova et al., 2005) an increase in the release of inflammatory mediators, hypersensitivity in bronchial cells and increased in vascular permeability (Katsumata et al., 1990). All of which lead to the development of asthma.

The second possible theory would be that the reduction of GSH in antigen-presenting cells leads to an increased level in Th1 and Th2 T-helper cells leading to an increase in the risk of an allergic response such as asthma (Peterson et al., 1998). This could be due to a combination of genetic (polymorphisms of the glutathione-S-transferase family, (especially those that have the GSTP1 Ile105Val variant) and environmental factors that increases susceptibility to asthma. The presence of this polymorphism has an increased risk of a bronchial hyper responsiveness to progress to asthma (odds ratio (OR) = 4.57, Confidence Interval (CI) = (2.43-8.57) in comparison to those that do not have the polymorphism (OR=1.4, CI= 0.58-3.39) with a significant p value of = 0.023 (p<0.05) (Imboden et al., 2008). Therefore gene-environment interaction and the role of T-helper cells in response to paracetamol also might contribute to the predisposition to asthma.

The third possible mechanism would be through the lack of COX-2. Paracetamol is thought to result in damage to the airway epithelium by being a COX-2 inhibitor. This is because COX-2 is thought to help protect the airway epithelium from injury (Henderson and Shaheen, 2013).

Another suggested mechanism that has been tested through a mouse-model would be that the use of paracetamol results in the production of NAPQI in the lungs (a toxic metabolite). NAPQI will then stimulate the transient receptor potential ankyrin-1 (TPRA) that triggers the inflammatory cascade in the airway (Henderson and Shaheen, 2013).

Lastly would be the role of genetics and epigenetics. It is known that the presence of certain genetic polymorphisms such as the GSTP1 increases the risk of wheezing, especially with paracetamol in fetal life. There has also been the theory that the epigenetic process of modified DNA methylation can increase the risk of the development of childhood asthma. This can possibly explain how the use of paracetamol in pregnancy can affect the fetus (Henderson and Shaheen, 2013).

Therefore, the mechanism is still uncertain and there are still doubts as to whether paracetamol actually does cause an increased risk of asthma. However, though there is a large amount of evidence that paracetamol may lead to asthma, as was mentioned in the Phase 3 ISAAC trials, more study needs to be done to prove this relationship through a placebo controlled clinical trial. Additionally, although there is a lack of definitive conclusion, we cannot dismiss the possibility of the biological interaction that can link paracetamol with asthma. Comprehending the mechanism of action of paracetamol itself might aid to understand its interaction in the asthma pathophysiology, which might help in understanding how it increases the risk of the development of asthma.

CONCLUSION

Through the literature, it is known that the use of paracetamol in early childhood life does present a certain risk to asthma. Although not thoroughly conclusive, there have been multiple studies that prove the correlation. In SCD, this can cause major difficulties, as the prognosis of SCD with a co-morbidity of asthma results in an increased risk of complications such as ACS that increases mortality.

Further studies should be done to confirm this correlation as well as the pathway that causes this link. Through this, more research can be done to develop an effective analgesia that does not precipitate the risk of asthma but still have tolerable side effects.
Another consideration would be to develop more treatment that targets the disease itself instead of providing pain relief. More research would have to be done to further understand the pathophysiology of SCD. Through this, more effective drugs that target the cause of the disease can be employed instead of symptom-relief.

There have been a number of progressions that have already been made in this direction. The first would be the use of hydroxycarbamide. Hydroxycarbamide increases HbF concentration in red blood cells, thereby reducing intra-erythrocyte precipitation of haemoglobin. Studies have also shown that in the long-term, hydroxycarbamide can reduce the number of painful episodes, ACS, hospitalisation and the number of blood transfusions required. Secondly, another method would be blood transfusions as blood red cell transfusion dilutes the HbS containing erythrocytes with normal erythrocytes and also improves anaemia. Additionally, blood transfusions reduce the risk of other complications such as stroke. Thirdly, would be the option of haemopoietic stem cell transplant. There are many concerns with regards to transplantation such as rejection, toxicities and risk of infection. However, a successful transplant does target the problem and prevents future VOE, ACS, stroke, and other complications of SCD in addition to improving the patient’s prognosis. Fourthly, would be the option of gene therapy. Although novel and still highly experimental, it holds promising results, to be able to insert the corrective gene into an RNA virus and letting the virus insert the gene safely into the patient’s DNA, correcting the pathological mutation (Ware et al., 2017).

In conclusion, the use of paracetamol in children with SCD comes with risks that can cause further complications such as asthma. Instead, we need to focus on further understanding SCD and targeting therapy towards the pathophysiology.

**BIBLIOGRAPHY**


ed. United Kingdom: Brent Sickle Cell & Thalassaemia Centre.


