The effects of nebulised β_2 agonists on clinical observations in asthma exacerbations

Abstract

Background: Despite concerns over their resultant side effects short-acting β_2 agonists are still used in high doses internationally in prehospital care delivery to treat asthma exacerbations. This systematic review set out to identify the physiological effects associated with this treatment and determine their potential impact on the patient's presenting or underlying conditions.

Methods: A systematic search of literature published from 2010 to 2020 and focusing on asthmatic patients receiving nebulised β_2 agonists during an acute exacerbation was undertaken with relevant articles reviewed.

Findings: Eight out of 897 studies met the inclusion criteria. Despite being heterogeneous with ranging outcome measures, synthesis showed evidence of bronchodilator action throughout, with reductions in potassium levels and cardiovascular changes reported across several studies.

Conclusions: Therapeutic effects demonstrated within the data support the use of nebulised β_2 agonists in these patients, and whilst adverse effects are frequently seen in the cardiovascular and endocrine systems, their impact on the patient's overall condition remains unclear.

Keywords:

- Asthma
- Nebulisation

- β_2 agonists
- Paramedic
- Pre-hospital

Key Points:

- Despite the potential for β_2 agonists to cause adverse side effects these are not observed in all patients.

- Cardiorespiratory changes are the most common effects seen when administering nebulised Salbutamol, whether because of selective or non-selective actions.

- The ventilation/perfusion balance experienced by asthma patients is such that a change to one component could result in a perpetuation of hypoxaemia which in turn could extend the exacerbation.

- With the potential for potassium levels to drop during and following treatment with β_2 agonists, an associated risk exists whereby blood glucose levels may demonstrate a reciprocal rise.

Questions:

- Considering the potential physiological links, what co-morbidities are asthma patients most likely to have?

- How can changes to electrolyte levels change the way patients present to clinicians during an exacerbation of their condition?

- Do asthma patients typically present as one of the three levels of severity stated within JRCALC guidelines?

Introduction

Asthma is a non-communicable respiratory condition that according to the 2016 Global Burden of Disease study affects an estimated 339.4 million people worldwide (GBD, 2017). Estimating 1000 global deaths per day from asthma, this same study calls it the '*tip of the iceberg'* when it comes to the overall impact of the condition (GBD, 2017). With an estimated 23.7 million disability-adjusted life years (DALYS) attributable to asthma globally during 2016, the morbidity of asthma poses the greatest burden to the daily functioning of those with the condition (GAN, 2018).

Currently with no definitive cure, an approach of symptom control and prevention of triggering factors has been shown to effectively reduce levels of morbidity and mortality (Papaioannou, et al., 2015; Oland, et al., 2017). The standard treatment for patients experiencing an exacerbation of their asthma has remained constant for almost forty years and involves the use of bronchodilator drugs (β_2 agonists) to relieve the bronchospasm associated with asthma (Sellers, 2013; Almadhoun et al., 2020).

However, in 2010 the Global Strategy for Asthma Management and Prevention (GSAMP) was updated to suggest that we should move away from Short-Acting β_2-Agonists (SABAs) as the primarily treatment for asthma exacerbations (GINA, 2010). This is a point that has been under discussion for many years given their potential to mask ongoing exacerbations and cause adverse short and long-term physiological changes (Billington et al., 2017; Martin et al., 2019). Despite this, clinical guidelines continue to state that clinicians should 'use high-dose inhaled β_2 agonists as first line agents in patients with acute asthma and administer as early as possible' (AACE/JRCAL, 2019; BTS, 2019).

Although targeted towards β_2 adrenoreceptors responsible for the relaxation of smooth muscle, the binding ability of SABAs is weak causing an 'off target' effect resulting in additional stimulation of the α_1, α_2, and β_1 adrenoceptors (Hsu et al., 2020). More commonly seen with the high dosages associated with pre-hospital care (Guhan, et al., 2000; Farzam

et al., 2020), the resulting physiological effects can result in changes within the cardiovascular, respiratory, nervous and endocrine systems which can alter their respective communication pathways (Chawla et al., 2016; Billington et al., 2017; Sampson et al., 2017; Hsu et al., 2020).

With such changes occurring within core systems the implications to the patients' presenting condition could be critical, and in the case of β_2 agonists, could oppose the intended therapeutic effects (Billington et al., 2017; Hsu et al., 2020). This may result in an extended exacerbation through perpetuation of the ongoing hypoxaemia (Chawla et al., 2016; Billington et al., 2017; Sampson et al., 2017; Hsu et al., 2020), as a direct result of compounding cardiac arrhythmias (Hsu et al., 2020) and reduction in oxygen saturations (Seifi et al., 2018).

By looking at the literature published since the GSAMP report this systematic review aimed to gain a better understanding of the physiological changes that occur in asthma patients as a result of using SABAs, any characteristics of treatment that may affect its results, and any adverse effects that could potentially impact the patient's short and long-term health.

Methods

Search Strategy

A search of literature from 1st January 2010 to 24th September 2020 was undertaken using PubMed, MEDLINE, CINAHL, EMBASE, Cochrane Library, Web of Science, TRIP and EThOS. A simplified search strategy derived from an initial scoping review and consolidated through Medical Subject Headings (MeSH) and Embase Emtree used the terms *'asthma'* and *'albuterol'* or *'salbutamol'* or *'Ventolin'* or *'beta 2'*. Filters were included on each database where possible, including the date range, age groups, English language, and human participants. Extensive manual filtering was then undertaken to ensure all studies met the systematic review's inclusion/exclusion criteria.

The review protocol was published on PROSPERO (Registration: CRD42020200131) during September 2020. An amendment was made during November 2020 relating to the exclusion criteria.

Selection Criteria

All studies that included diagnosed asthmatics treated with nebulised SABAs as part of the methods were considered. Studies had to directly relate to this review's aims by reporting on changes to the cardiac and respiratory systems and/or identifying biological characteristics that alter the mechanism of action of nebulised β_2 agonists.

Studies were excluded from the review if: a) patients were treated with β_2 agonists for conditions other than asthma (e.g. COPD); b) long acting β_2 agonists were used (e.g. salmeterol); c) other drugs were used alongside the β_2 agonists to treat the exacerbation (e.g. hydrocortisone or Ipratropium Bromide); d) the study included pregnant women; e) the study included children under 5 years of age; e) low dose therapy or delivery methods other than nebulisation were used (e.g. inhaler).

All papers meeting the inclusion/exclusion criteria were included irrespective of methodology. Abstracts and systematic reviews were not included within this process. Final papers had their references checked to identify any eligible studies that may have been missed during the initial review.

Data Extraction

Data extraction was undertaken independently by two reviewers using a modified version of the Cochrane Collaboration Library 'Data collection form' (EPOC, 2013). The same reviewers assessed risk of bias and quality using the Cochrane Collaboration 'Risk of Bias' tool (EPOC, 2013; EPOC, 2017) and a modified version of the Critical Appraisal Skills Programme (CASP) cohort study checklist (CASP, 2018).

Data Analysis

A narrative synthesis was used to report the findings using a descriptive approach due to the heterogeneity of studies' (Kim, 2017). Categories were derived from study characteristics and results to assist with the identification and contextualisation of specific themes (Nowell et al., 2017), offering the maximum level of comparison.

Results

Eight studies were eligible for synthesis. There was considerable variation in methods and reported outcome measures (Table 1) and often only partial datasets were relevant to the review, resulting in limited comparable data. Furthermore, following appraisal, just two studies demonstrated a low risk of bias and high level of quality (Table 2).

Table 1. Study Characteristics.

Table 2. Bias and Quality Assessments.

The flow of records through the review process is presented in Figure.1.

Figure 1. PRISMA algorithm.

Demographics

Of the eight studies only Mangunnegoro et al., Barkiya et al. and Ozer et al. included children (<18 years). The other five studies focused on the adult population although it is unclear in the Lorensia et al. study whether their youngest participants were 17 or 18 years old. However, only the Ozer et al. study subdivided the sample into age groups, removing the ability to use age as a comparable variable.

Drug Administration

All studies administered salbutamol, rather than alternative SABAs. Though three studies did not specifically state (Sahan et al., Barkiya et al., Lorensia et al.), it is expected that seven of

the studies used oxygen-driven nebulisers given their setting, whilst Mangunnegoro et al. used a compressor nebuliser. All adult-only studies used a repeat dose of 5mg with those involving children using a lower dose of 2.5mg or a weight-based dose of 0.15 mg/kg. Lorensia et al. did not identify the dosage used. Six studies administered the drug over 20-minute increments, Hazra et al. uses 30-minutes increments and Lorensia et al. do not specify any timings.

Clinical Observations

All studies undertook their measurements at baseline and at least one other timepoint post-drug administration, either after each dose or after the final dose. The observations and results are shown in Table 3.

Table 3. Terse Study Results

Blood Oxygenation

Ozer et al. and Barkiya et al. recorded peripheral capillary oxygen saturation levels using a pulse oximeter (SpO2) and Mangunnegoro et al. and Hazra et al. used blood samples to gain arterial oxygen saturation levels (SaO2). Both Ozer et al. and Barkiya et al. demonstrated a trend towards an improvement in SpO2 during treatment, although Ozer et al. reported salbutamol-induced hypoxia following the initial dose. Hazra et al. used SaO2 and just stated that '*oxygen saturation was almost within normal ranges'* without further clarification. Mangunnegoro et al. demonstrated a slight reduction in mean SaO2 between baseline and 120 minutes.

Lung Function

Das et al., Mangunnegoro et al., Hazra et al. and Nabi et al. measured Peak Expiratory Flow Rate (PEFR) and Barkiya et al. Forced Expiratory Volume (FEV1). In all, improved lung function was suggested by increases from baseline following each dose.

Heart Rate/Respiratory Rate

Baseline and post treatment heart rate (HR)/respiratory rate (RR) figures were reported only within the Barkiya et al. study, reporting an improvement in RR and the presence of a significant tachycardia after all doses. Ozer et al. and Mangunnegoro et al. both recorded HR/RR for use as part of their scoring system, with Mangunnegoro et al. further stating the presence of tachycardia within ECG traces at 120 minutes. The Hazra et al. study did state that an increase in pulse and RR was seen, although no figures were attributed.

Asthma Scoring

Mangunnegoro et al., Barkiya et al. and Ozer et al. all used a scoring tool to assess the severity of the presenting exacerbation at baseline and post treatment. Though these tools differed, they shared common variables; Barkiya et al. used the Clinical Asthma Severity Score (RR, oxygen saturations, wheeze, retractions, dyspnoea); Ozer et al. the Modified Pulmonary Index Score (HR, RR, oxygen saturations, wheeze, accessory muscle use, inhalation-exhalation ratio); and Mangunnegoro et al. used a tool based on the Global Initiative for Asthma (GINA) 1998 criteria of breathlessness (HR, RR, wheezing, breathlessness, talking, alertness, accessory muscles and suprasternal retractions, peak expiratory flow rate). All three studies demonstrated a reduction in severity from baseline, suggesting nebulised salbutamol does reduce the severity of the presenting asthma exacerbation.

Sodium/Potassium Levels

Sahan et al., Barkiya et al. and Lorensia et al. recorded serum potassium levels with Lorensia et al. also measuring sodium levels. All three studies showed a decrease in potassium levels for the majority of patients with Barkiya et al. demonstrating a significant decrease (0.5-0.8 mEq/L from baseline values) in 70% of participants following nebulisation. Lorensia et al. reported an inconclusive range of changes in sodium levels. These data strongly suggest a correlation between the administration of salbutamol and reduction in serum potassium to a potential level of hypokalaemia.

Patient Reported Side Effects

Half of the studies identified patient-reported side effects (Das et al., Mangunnegoro et al. Hazra et al. and Nabi et al.). These included headaches, tremors, palpitations and nausea/oral irritation. Although not definitive, the numbers indicate that at least 10% of those receiving repeated doses of 5mg salbutamol experienced some form of patient-identifiable side effect, but where lower doses were used this frequency was reduced.

Comorbidities

Mangunnegoro et al. Lorensia et al. and Ozer et al. specifically identified participant comorbidities. The Mangunnegoro et al. study excluded diabetic patients. Ozer et al. mentioned conditions that predominantly present alongside asthma as part of the Immunoglobulin E (IgE) sensitisation pathway whilst Lorensia et al. identified one participant with diabetes, one with raised cholesterol and one with gastritis. The patient with diabetes demonstrated hypokalaemia following treatment but with only a single study that involved three participants with conditions that sit outside the IgE pathway, no relationship can be identified between diabetes and potassium levels.

Discussion

Recent years have seen significant discussion around how best to manage asthma exacerbations and there is debate on the appropriateness of using SABAs. However, guidelines developed for UK ambulance services continue to support their repeated use as the first pharmacological step in managing these acute events (AACE/JRCAL, 2019; BTS, 2019).

Characteristics

Key characteristics for review in this study were dosage, age and recorded outcomes. The age demographic is important given the pathogenesis of asthma and how patients seem to

outgrow the condition or develop it in later life (Warke et al., 2002; Trivedi et al., 2019). Only patients ≥5 years were included within the review but investigation of age as a variable was not possible as only one study subdivided participants by age. Children did receive a lower dose, compared to adults and studies that monitored clinical observations throughout the treatment timeframe demonstrated the effects of a cumulative dose upon cardiovascular and respiratory observations in line with evidence produced by previous studies (Sellers, 2013). Only a general conclusion can be made from our review of these study characteristics and that is that most asthma patients ≥5 years respond similarly to the administration of nebulised salbutamol when aligned with the dosing recommendations of the National Institute for Health and Care Excellence (NICE, 2021).

Changes in Clinical Observations

Those studies using lung function testing and asthma scoring as an indicator of the effectiveness of Salbutamol reported improvements through the course of treatment. This supports the rationale for administering SABAs to asthmatics, but does not contribute to the overall understanding of the drug.

Current guidelines suggest that arrhythmias, especially tachycardia, are frequent side effects seen in patients receiving SABAs (AACE/JRCAL, 2019; BTS, 2019; NICE, 2021). Despite this, several studies failed to record/report the HR, suggesting that its importance in the overall rating of the exacerbation is often underestimated (Rolfe, 2019; Sapra et al., 2020). Whilst only three studies reported this parameter, they all noted an increased HR, supporting the previous incidences where this has been recorded (Sears, 2002; Cazzola et al. 2013).

Disruption to the cardiovascular and respiratory systems can result in a lung ventilation/perfusion ratio (V/Q) mismatch (Petersson et al., 2014; Sarkar et al., 2017) and the result of this change is seen through a reduction of blood oxygenation levels. Whilst SaO2 is generally regarded as the gold standard for assessing oxygenation levels (Bilan et al., 2010; Chan et al., 2013) the convenience of SpO2 monitoring makes it the first choice for

ongoing patient assessment in the prehospital setting. However, the use of SpO2 to provide definitive values has been questioned, given its potential to either underestimate or overestimate readings (Muñoz et al., 2008; Chan et al., 2013; Amalakanti et al., 2016) as a result of poor peripheral circulation or external factors, such as skin temperature and movement (Bilan et al., 2010; Guler et al., 2016). The selected studies demonstrated the presence of reduced blood oxygenation levels and do suggest an increase follows drug administration over a 60-minute timeframe. Although, some individuals may also demonstrate a reduced level of oxygenation following initial treatment for reasons not explained, further indicating that oxygen levels are transient depending upon age and severity of exacerbation (Gleeson et al.,1988). Furthermore, the level of V/Q mismatch could be such where a correlation between SaO2 and SpO2 may not be instantaneous, given the reactionary mechanisms during hypoxia that result in peripheral shutdown of the circulatory system in order to prioritise core tissue such as the heart/brain (Seifi et al., 2018; Chan et al., 2013).

In line with current literature/guidelines the studies show that both favourable and adverse effects are most commonly seen within the cardiac and respiratory systems with a clear understanding of their cause (Hsu et al., 2020). However, other effects reported by the studies are less obvious and may impact the patient's condition in more varied ways. The decrease in serum potassium levels (Sahan et al., 2013; Barkiya et al., 2016; Lorensia et al., 2016) is an effect widely reported in past studies (Heianza et al., 2011) and, in fact, this mechanism may be used therapeutically for patients presenting with hyperkalaemia (Viera, 2015). Although potassium is key to ensuring electrical functions such as muscle stimulation and nerve impulses are maintained within suitable limits (Udensi et al., 2017), its change in the short term is not usually problematic. However, when levels reach that of hypokalaemia and are present longer-term, wider functions including those within the respiratory, cardiovascular, endocrine, and nervous systems may be affected (Udensi et al., 2017). This trigger, secondary to that of receptor stimulation, can result in the more commonly seen

adverse effects of β_2 administration such as arrhythmias, palpitations, headache, muscle twitching, malaise and subdued insulin production and tolerance (Heianza et al., 2011; Petersson et al., 2014; Udensi et al., 2017; NICE, 2021).

With these cardiac and electrolyte changes, the potential for asthma patients already experiencing a level of V/Q mismatch to be impacted to a greater degree is high (Sarkar et al., 2017). It may also explain why caution may be required when administering β_2 agonists to diabetic patients, given the potential for blood glucose levels to rise as a result of retarded insulin production or action thereof (Jacques et al., 2013). This is something one study alluded to when a diabetic participant presented with hypokalaemia following treatment, although given the high bias and low-quality assessment of this study the potential correlation between diabetes and potassium levels cannot be corroborated.

So, whilst the presented data continues to support the therapeutic benefits of SABAs in the management of asthmatics, it is also clear that changes to HR and electrolyte levels accompany these effects. However, despite both having the potential to affect patients whether they have underlying medical conditions or not (Sevransky, 2009; Udensi et al., 2017), none of the included studies reported on whether the adverse effects of β_2 agonists impacted the patients' underlying health conditions. This leaves a gap in our understanding given the range of potentially compounding health conditions that may be present. Future studies need to investigate these potential associations and the significance of any links identified.

Implications for Practice

This review highlights the limited data available to make any definitive conclusions about the use of β_2 agonists in the treatment of asthma exacerbations. However, there is sufficient to suggest that some patients may experience potentially significant adverse effects that are not commonly identified, considered or reported.

Further investigation of the full effects of nebulised β_2 agonists and how different patients react to the drug during an acute exacerbation will help optimise future treatment for the asthmatic population. Any actionable findings could assist with limiting adverse effects, potentially reducing levels of hypoxaemia, hypokalaemia and exacerbation times.

Limitations

The inclusion/exclusion criteria used in this review resulted in a small heterogenous sample of articles and, at times, in partial data sets being abstracted, thereby reducing the scope for comparison across studies.

Of the data sets identified there were inconsistencies that further decreased the level of comparison and correlation that could take place. This can be seen where, despite the subject matter, a number of studies did not report on basic clinical observations such as HR and RR, both crucial markers in assessing the severity of exacerbation (Aldington, 2007).

Even when clinical values were assessed across multiple studies a difference in testing techniques again reduced the overall level of comparability, for example, the variation in measures of blood oxygenation.

Additionally, the overall quality and risk of bias attributed to the majority of the studies has resulted in a lower confidence in effect of the true value of any outcomes. It is however accepted that whilst the Cochrane 'Risk of Bias' tool was used to assess the studies, the additional appraisal tool, although widely established, was modified to include a numerical rating system. Although this did not alter the focus of the tool it may reduce its validity within this review.

Conclusion

This systematic review supports the use of SABAs in patients experiencing an uncontrolled exacerbation of their condition. A clear post treatment reduction in exacerbation severity and improvement in overall lung function has been shown throughout. It has not been possible to establish the level, frequency and range of adverse effects, although the non-selective nature of β_2 agonists can be seen within the functionality of both the cardiovascular and endocrine systems. Despite asthma being associated with non-related co-morbidities, it is unclear how these conditions may be affected by any of the identified adverse changes, although variations in HR, electrolytes and oxygen saturation levels can all impair normal physiological functions. Additional research is required to understand the complexities of the systemic and non-systemic changes experienced by asthma patients receiving nebulised SABAs, with a focus on how these manifest and impact upon underlying conditions.

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