Commentary

Asthma and PM_{10}

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Abstract

PM_{10} (the mass of particles present in the air having a 50% cutoff for particles with an aerodynamic diameter of 10 μm) is the standard measure of particulate air pollution used worldwide. Epidemiological studies suggest that asthma symptoms can be worsened by increases in the levels of PM_{10}. Epidemiological evidence at present indicates that PM_{10} increases do not raise the chances of initial sensitisation and induction of disease, although further research is warranted. PM_{10} is a complex mixture of particle types and has many components and there is no general agreement regarding which component(s) could lead to exacerbations of asthma. However pro-inflammatory effects of transition metals, hydrocarbons, ultrafine particles and endotoxin, all present to varying degrees in PM_{10}, could be important. An understanding of the role of the different components of PM_{10} in exacerbating asthma is essential before proper risk assessment can be undertaken leading to advice on risk management for the many asthmatics who are exposed to air pollution particles.

Keywords: air pollution, asthma, exacerbation, PM_{10}

Introduction

There has been a trend towards an increase in both prevalence and exacerbations of asthma throughout the late twentieth century, at a time when the issue of air pollution has come to the fore in public and scientific awareness. It is therefore reasonable to ask whether there is a relationship between the two. Among the constituents of the air pollution cocktail, the particles or PM_{10} component is considered to be a significant culprit in terms of mediating adverse health effects [1]. This commentary focuses on the relationship between particulate air pollution and asthma.

PM_{10}

The average UK city has 20–25 μg/m^3 PM_{10} in the air, but excursions to higher levels occur regularly [2]. The PM_{10} convention describes the mass of particles per unit air volume that deposit in the upper and lower airspaces, but excludes those that are so large that they deposit only in the nasopharynx.

Trends in asthma occurrence and in particulate air pollution

This topic has been dealt with in detail in a monograph by the UK Committee on the Medical Effects of Air Pollution

PM_{10} = mass of particles present in the air having a 50% cutoff for particles with an aerodynamic diameter less than 10 μm.

[3]. There has been an increase in asthma, as measured by wheeze, GP consultations or hospital admissions, throughout the 1960s and up to the end of the 1990s. At the same time air quality has improved because of stricter control on industrial and domestic emissions ([3]; see also http://aeat.co.uk/netcen/airqual/ for an excellent summary of the UK experience of air pollution in the past 10 years). However, despite the overall decrease in total mass of airborne particulates, the number of vehicles in the UK has increased twofold to threefold over the past 25 years, and concentrations of very small, combustion-derived particles have actually risen during this period [4].

The relationship between PM_{10} and asthma

Asthma is a form of allergic lung disease that features an accumulation of inflammatory cells and mucus in the airways, with bronchoconstriction and a generalised airflow limitation. The induction phase of the disease arises from interactions between allergenic proteins and immune cells. Subsequent exposure to allergens then results in a complex cascade of mediators, which produce airway narrowing and inflammation. In addition to having a heightened sensitivity to allergens, asthmatics also develop non-specific hyper-responsiveness to a wide variety of stimuli including cigarette smoke, sulphur dioxide, hypertonic saline and cold air. Many studies have demonstrated that acute increases in PM_{10} result in a greater use of asthma medication, more consultations of GPs and increased hospital admissions for asthma [5–9]. Such data are typically expressed as the percentage increase in, for example, asthma symptoms per 10 $\mu g/m^3$ increase in PM_{10}. A recent review [10] describes an average 2% increase in hospitalisations and related health care visits, and an approximate 3% increase in asthma symptoms for each 10 $\mu g/m^3$ rise in PM_{10} as the average across a number of studies. In clinical studies, normal and ragweed-sensitive human volunteers exposed to diesel exhaust via the nose produced more allergic IgE antibody [11]. However, there are studies that show a much less clear picture of the association between PM_{10} and symptoms [12].

In contrast with the association between levels of air pollution and exacerbations of symptoms in asthmatic individuals seen in many (but not all) studies, the role of air pollutants in the development of disease is controversial. The large six-city study in the USA found no association between the incidence of asthma and the level of airborne particulates [1]. Comparative studies between East and West Germany showed that the point prevalence of asthma was higher in West Germany, whereas industrial air pollution and levels of bronchitis were higher in East Germany [13]. Finally, asthma rates have also risen in other areas of the world (eg New Zealand) where there are far lower levels of air pollution than the USA and Europe.

Although this last point illustrates that the increasing incidence of asthma is not dependent on ambient air quality, the effect of exposure to air pollutants on allergic sensitisation has not been categorically ruled out. Several studies in Europe and Japan have reported an increased frequency of allergic sensitisation in individuals living in urban areas or close to highways and therefore exposed to higher concentrations of vehicle exhaust [14]. In addition, a more recent analysis of respiratory allergies between polluted and 'clean' counties in East Germany has found a strong association between sensitisation rates and amounts of air pollution [15]. Finally, the fact that children exposed to second-hand smoke have a doubled risk of developing asthma [16] suggests that insult to the respiratory tract might promote allergic sensitisation.

The toxicology paradigm as it applies to PM_{10} effects

The central paradigm of toxicology is exposure → dose → response. We shall discuss these in turn in relation to PM_{10} as the dose, and asthma as the response.

PM_{10} is not a single entity but represents all particulate matter collected by the sampler from its immediate surroundings at the sampling site. Therefore PM_{10} from a rural site is largely windborne crustal material, while that from a city centre would largely comprise vehicle-derived particulates such as diesel soot. When site-specific variability is superimposed on seasonal, climatological and global location it becomes clear that PM_{10} is a heterogeneous mixture of particle types. However, toxicologists have identified several components of PM_{10} such as transition metals [17], ultrafine particles [18] aromatic hydrocarbons [11] and endotoxin [20] that may be important in driving the adverse effects.

The normal PM_{10} in the UK is around 25 $\mu g/m^3$ of air. This is a very low concentration of airborne particulate compared with occupational settings such as mining and some agricultural practices, in which the exposure can be up to 4000 $\mu g/m^3$ respirable dust. The association of adverse health effects with such low ambient exposures is thought to be due to the susceptible nature of the populations that are affected by PM_{10} such as asthmatics [10]. It is also becoming clear that the mass of PM_{10} might not be the best metric for describing the harmful fraction of airborne particle. The total mass is usually dominated by larger secondary particles such as sulphates and nitrates, which are generally considered to be of low toxicity, whereas the mass contribution of metals, organics, ultrafine particles or endotoxin is much less.

Dose

Effective dose is the concentration of a substance that mediates adverse effects and is of fundamental importance with a heterogeneous material such as PM_{10} for the

successful performance of a risk assessment. In the case of an endpoint such as an asthma attack, the effective dose is likely to be the dose of particles that causes cells to release substances such as pro-inflammatory and immunoregulatory cytokines, lipid mediators, enzymes and reactive oxygen species, which enhance immune and inflammatory responses. Alternatively, in conjunction with exposure to allergens, the effective dose could be the concentration of particles that allows increased interaction between antigen and immune cells, as would occur via changes in epithelial permeability or by eliciting greater numbers or activities of immunocompetent cells.

Air pollution particles can be divided roughly into those that are formed immediately by combustion sources such as diesel exhaust, which are carbon-centred, relatively small in primary particle size and essentially insoluble. Another principal type of particle is those created via chemical reactions in the atmosphere, which arise as condensation nuclei containing the familiar soluble components of PM_{10} such as sulphate and nitrates [2] and which can grow according to climatic conditions. The carbon-centred primary particles are considered to be most potent in terms of their ability to cause lung injury. They could be important for at least two reasons: first, they can contain surface transition metals that can redox cycle in the lung and generate harmful oxidants [17], and second, they are in the ultrafine size range (less than 100 nm in diameter), a size range that has been shown in numerous toxicological studies to have enhanced toxicity [19].

The common pathway of oxidative stress is another potential harmful dose, although one that has to be considered as different from the inherent properties of the particles such as size or composition. Oxidative stress can be seen as a function of the both the particle and the lung milieu. The particle might contribute transition metals, whereas the lung milieu supplies reducing activity in the form of such molecules as glutathione and ascorbic acid, which allow the transition metals to redox cycle. The antioxidant defences of the lung will tend to protect against the oxidative stress. Ultrafine particles might have their effects via oxidative stress that arises from their large surface area and particle number per unit mass, interacting with elements of the lung milieu.

Responses

Asthma is a complex disease whose symptoms include wheezing, chest tightness and recurrent cough. Other markers of the disease include the presence of IgE in allergic asthmatics, increased numbers of eosinophils in blood and tissue, and hypersecretion of mucus. Although many of these features can be aggravated by pollutant exposure, the complex nature of the asthmatic response and the huge array of mediators that contribute to airway disease precludes identifying one single mechanism for pollutant-enhanced illness. Rather, several different pathways have been proposed that contribute to the asthmatic response and which could be amplified by PM exposure. These include the ability to cause inflammation with subsequent tissue damage, increased translocation of antigen to immune cells with subsequent increases in immune-mediated disease, neurogenic stimulation with increased smooth muscle constriction and airway inflammation, and direct stimulation of lipid mediators and mucus, which contribute to airway narrowing and blockage respectively.

The role of oxidative stress

The pathways arising from oxidative stress are known to be important in asthma [21] and in inflammation in general, and the redox-sensitive transcription factors NF-κB and activator protein-1 (AP-1) are important in controlling the expression of pro-inflammatory mediators [22]. We have reported that oxidative stress can be detected systemically in asthmatics and that it worsens during an asthma attacks [23]. PM_{10} is known to generate free radicals via transition metal mechanisms [24] and has been reported to cause oxidative stress in rats after pulmonary instillation [25]. Additionally, cells treated with PM_{10} *in vitro* show activation of NF-κB and AP-1 by pathways that involve the generation of hydroxyl radicals by Fenton-type chemistry [26]. The imposition of an additional oxidative, pro-inflammatory burden on the airway mucosa by depositing PM_{10} during a period of increased particulate air pollution could therefore be important in triggering an asthmatic attack.

Conclusion

PM_{10} is the particulate component of air pollution that can enter the lungs, deposit in the airways and also penetrate to the periphery of the lungs. There is good epidemiological evidence that asthma symptoms can be worsened by increases in PM_{10} but less evidence at present that PM_{10} increases the likelihood of initial sensitisation and induction of disease, although this matter requires further study. Although PM_{10} is a complex mixture of substances, toxicological studies have identified a number of components that could render the dose of PM_{10} effective in enhancing inflammation and causing oxidative stress. These include transition metals, hydrocarbons, ultrafine particles and endotoxin. A clear understanding of the effective dose of PM_{10} that can trigger or exacerbate asthma attacks is essential before proper risk assessment can be undertaken. This will provide much-needed advice directed at risk management for the increasing numbers of asthmatics who are potentially exposed. Well designed toxicological studies will provide a better understanding of the constituents and concentrations that make PM_{10} a hazard to asthmatics.

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