Clinical Toxicology and Its Relevance to Asthma and Atopy

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KEYWORDS

• Asthma • Bronchoconstriction • Opiate • Mast cell • Degranulation • Heroin • Insufflation

KEY POINTS

- Both licit and illicit opiates have effects on the immune and neurologic components of asthma inflammation and clinical disease.
- How these effects summate determines the clinical output of this complex interplay, with either worsening or improvement of asthma.
- Laboratory toxicology/drug monitoring of patients can provide clinicians with objective information to facilitate appropriate prescribing and management determinations.

There are notable increases in the use of prescription pain relievers, substance use disorder treatment admission rates, and prevalence of asthma. The overall US prevalence of asthma increased from 7% of the general population in 2001 to 8% in 2010.[1] Select population demographics may have a greater prevalence in that the Black non-Hispanic population approaches 10% and the Puerto Rican subset of the Hispanic demographic has been reported at 16.5% in 2004.[1] The sales of prescription pain relievers in 2010 were 4 times those in 1999, and the substance use disorder treatment admission rate in 2009 was 6 times the 1999 rate.[2] The overdose death rate in 2008 was about 4 times the 1999 rate.[2] Fortunately, asthma death rates have leveled off in recent years.[1] However, increased asthma mortality rates are higher in women, Black persons, and adults.[1] The prevalence of asthma is greater for women (9.2%), than men (7.0%).[1] Women are more likely to have chronic pain, be prescribed prescription pain relievers, be given higher doses, and use them for longer periods than men.[3] Further, women may become dependent on prescription pain relievers more quickly than men.[3] Recent data from the Centers for Disease Control and

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Prevention have shown the greatest increase in epidemic of prescription drug overdoses from 2013 to 2014 occurred among non-Hispanic Black (8.2%), versus non-Hispanic White (8.0%) women and no change (0%) among Hispanics.[3] Taken together, both asthma and prescription pain reliever abuse are increasing and may disproportionately affect non-Hispanic Black women.

Drug overdose is the leading cause of accidental death in the in the United States, with 47,055 such deaths in 2014, with 18,893 overdose deaths related to prescription pain relievers.[4,5] There is a yin-yang interaction regarding the use of opiate analgesics with asthma pathophysiology and clinical course, which may be contributing to the current epidemic of opiate analgesic deaths.

In a recent review of hospitalizations among inner-city adults,[6] of 11,397 patients admitted in Chicago or Cleveland from 2005 to 2008, 3% were dependent on inhalational heroin. Heroin-dependent patients were 3 times more likely to be admitted for respiratory problems, compared with nondependent patients. This relationship was more striking for those with asthma exacerbations (odds ratio of 7.0).[6] Of 23 inner-city patients admitted to an inner-city intensive care unit with asthma exacerbations,[7] 56% describe asthma exacerbations associated with heroin insufflation. A 1996 review of fatal asthma in the same inner-city setting found that about a third of cases were confounded by substance abuse or alcohol,[8] which was roughly the same proportion as those dying from homicide. Asthmatic patients whose asthma death is confounded by opiate use are more likely to be older, have no immediate respiratory complaints before the event, and to be found dead.[9] Inhalation of heroin with cocaine has been linked to measurable airway hyperreactivity, which persists after the cessation of this substance abuse,[10] and, therefore, might contribute to ongoing bronchospasm and asthma activity.

These reports of the effects of illicit opiate use on asthma clinical disease activity are not complemented by studies of the effect of licit opiate use on asthma, which is an understudied area. In 2014 more people died of drug overdoses the United States than any previous year on record.[4] Approximately two-thirds of these involved opioids. These opioid deaths involve 2 trends: an increase in heroin use as well as a 15-year increase in deaths from prescription opiates, including fentanyl and tramadol. There is an increased availability of illicit fentanyl.[11] Although rare, licit fentanyl has been reported to cause asthma[12,13] and cough.[14]

The pediatric population warrants additional consideration. Asthma prevalence is greater in children in general than adults (8.6% for those younger than 18 years compared with 7.4% in adults) and is greater in select populations: 13.4% in the Black non-Hispanic populations and 23.5% in the Puerto Rican subset of the Hispanic population.[1] Differences in physician gender and perception may bias referral to a pulmonologist compared with maintenance in a primary care setting as well as opioid prescribing habits for pediatric asthma and pain management.[15] Further, in a study of patients' opioid misuse, providers were more likely to assess African American patients, younger patients, and patients with a history of illicit drug use as likely to have misused prescribed opioids. However, this perception was not correct; only the patients who had a history of illicit drug use reported opioid misuse.[16]

In addition, in the pediatric population (12–17 years old), the prescribing rates for prescription opioids among adolescents and young adults nearly doubled from 1994 to 2007. In 2014, an estimated 28,000 adolescents had used heroin in the past year, and an estimated 16,000 were current heroin users. Most adolescents who misuse prescription pain relievers are given to them for free by a friend or relative; individuals often share their unused pain relievers, unaware of the dangers of nonmedical opioid use.[17] Thus, the relationship of opioid use and asthma in the pediatric population may exacerbate the risks over and above the adult population.

There is a yin-yang effect of opiates on respiratory processes, which can result in poor outcomes but can also be of clinical benefit. Opioids are potent respiratory depressants,[18] which is the leading cause of death from their overuse.[19] Yet opioids are also useful in the management of cough[20] and dyspnea associated with heart failure and chronic obstructive pulmonary disease.[21,22] Stimulation of opioid receptors located in the airways has varying effects, from inhibition of tachykinergic and cholinergic mediated constriction to inhibition of mucous secretion.[23] Codeine has been isolated from Chinese herbal antiasthma proprietary remedies[24]; a benefit for such addition of codeine may arise, in part, from the antitussive properties of codeine.

Morphine sulfate has been shown to decrease airway hyperreactivity of mild asthmatics to the same degree as atropine[25] and decreases cholinergically mediated bronchoconstrictive responses to sulfites (sulfur dioxide).[26] A study of the safety of a novel inhalation delivery system for morphine for pain control found that asthmatic patients did not have worsening of their disease from delivery of morphine through a pulmonary route.[27] Similarly, morphine has been found to be safe in treating asthmatic patients who require ventilator support.[28]

Mast cell activation is a central process in asthma pathogenesis.[29] Opioids release histamine from mast cells to varying degrees; codeine, morphine, and meperidine have the greatest histamine-releasing capability, whereas tramadol, fentanyl, and remifentanil do not release histamine.[30] In a study using intradermal microdialysis of human skin, only codeine and meperidine induced mast cell activation with release of tryptase and histamine, whereas fentanyl and other derivatives did not.[31] As naloxone did not attenuate the degranulation and release of tryptase and histamine, the investigators suggested that it is unlikely that μ-opioid receptors are involved in the activation of mast cells.[31] However, intravenous morphine and nalbuphine given to patients for general anesthesia have been found to increase plasma histamine levels.[32] Histamine is released from porcine mast cells in response to oxycodone but not to morphine or hydromorphone[33]

Opiate-induced histamine release might help to understand the development of status asthmaticus in illicit drug users.[8,34] Inhalational studies of the effect of codeine on bronchoconstriction found a significant effect in 11 of 17 adult asthmatic subjects, who were also highly sensitive to histamine inhalation challenge.[35] This effect was not reproduced by codeine administered by mouth or spraying of the buccopharynx. Skin responses of these subjects to histamine and codeine were no different in those who responded to inhaled codeine when compared with those who did not.[35] The investigators suggested that the codeine effect might be directly due to μ receptors in the bronchi.

Studying the effects of naloxone, an opiate receptor agonist[36] on asthma provides an alternate approach to assessing the effect of opiates in asthma pathogenesis. The Food and Drug Administration approved a naloxone auto-injector on April 3, 2014 for adults and children, as a new therapy to treat opiate overdoses.[37] However, there are reports that opiate antagonism might worsen asthma and precipitate increased mast cell activation. Allegretti and colleagues[38] reported cases of deterioration of asthmatic patients with exacerbations who, after receiving naloxone, developed respiratory failure from status asthmaticus. Similarly, Tataris and colleagues[39] reported that 2 of 21 patients (~10%) with possible heroin-induced bronchospasm who received nebulized naloxone as a treatment had worsening of their bronchospasm. Such worsening of bronchospasm might be attributed to withdrawal-associated anxiety,[40] which itself might be associated with hyperventilation. As hyperventilation invokes the bronchoconstriction associated with exercise,[41] it may play a role in the anxiety-associated worsening of asthma.

Opiate withdrawal by injection of naloxone to morphine-dependent mice increases the concentration of mast cells in the thalamus.[42] Although the effects of opiates on immunoglobulin E (IgE) production are not known, in murine models chronic administration of naloxone is associated with decreased interleukin (IL)-4 production, with increases in IL-2 and interferon-γ production,[43] suggesting that this opiate antagonist induces a shift away from the T helper 2 (Th2) cytokines associated with IgE production.[44] In contrast, studies by Roy and colleagues[45] report that morphine increases anti-CD3/CD28 antibody induction of CD4+ T-cell IL-4 protein synthesis as well as IL-4 mRNA and GATA-3 mRNA accumulation.[45] Taken together, these findings strongly suggest that opiate use is associated with increased Th2 responses and may increase both IgE and allergic responses. This finding is in concert with observations of a patient who developed persistent exacerbation of underlying stable asthma after initiating fentanyl transdermal therapy for chronic low back pain. Laboratory investigations were remarkable for slightly elevated serum IgE levels and progressively increasing eosinophils, which resolved within 72 hours on removal of the offending agent. Testing for IgE to specific opioids may be helpful in diagnosis but are not readily available.[12]

It may be prudent to assess opioid ingestion in asthmatic patients, via urine drug testing (UDT), as a means to obtaining a patient's objective narcotic/analgesic drug footprint to assist in the diagnostic workup and before prescribing additional pharmacopeia. This relationship between opioids and asthma may be more pronounced in pediatric and adolescent medicine whereby Saroyan and colleagues[46] reported that 22% of patients prescribed analgesics were nonadherent. Factors associated with nonadherence included being prescribed opiates and older age ($\geq$18 years old). In those studies, 50% of those nonadherent patients were identified through self-report and 50% via UDT.

Taken together, there is a mixed effect of opiates on the pathophysiologic processes involved in the airway inflammation that results in clinical asthma. Although there is anecdotal evidence of worsening of asthma with illicit opiate use, there is a clinical benefit with antitussive effects and relief of dyspnea with licit opiate use short-term. Whether there is exacerbation of asthma and worsening of allergic responses when either licit or illicit opiate compounds are used long-term has yet to be determined. In concert with this understanding, toxicologic assays (UDT) to elucidate the relationship between use of an opiate, either licit or illicit, with asthma activity and allergic responses would further aid in monitoring the interaction between drug use and associated asthma and allergy.

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