Heroin Insufflation as a Trigger for Patients With Life-Threatening Asthma*

Anne J. Krantz, MD, MPH; Ronald C. Hershow, MD, MPH; Nikhil Prachand, MS; Dana M. Hayden, MPH; Cory Franklin, MD; and Daniel O. Hryhorczuk, MD, MPH

Study objectives: **To determine the prevalence of self-reported, heroin-associated asthma symptoms among inner-city patients treated for life-threatening asthma, and to compare the rates of drug use between ICU patients with asthma and ICU control patients with diabetic ketoacidosis (DKA).**

Designs: **Study 1 was a sequential case series of patients requiring ICU admission for asthma (January to June 1999). Study 2 was a retrospective, case-control study of drug use among asthma patients and control subjects with DKA requiring ICU care (1997 to 1998).**

Setting: **Inner-city, public hospital ICU.**

Patients: **Twenty-three patients (26 ICU admissions) with asthma (age range, 16 to 50 years) admitted to the ICU from January to June 1999, and 84 patients (104 ICU admissions) with asthma and 42 patients with DKA (age range, 15 to 50 years) admitted to the ICU during 1997 to 1998.**

Outcomes studied: **Self-reported, heroin-associated exacerbations, history of heroin or cocaine use, and urine drug screen (UDS) results.**

Measurements and results: **In the sequential ICU admissions, 13 of 23 patients (56%) described asthma exacerbations associated with heroin insufflation. In the case-control study, asthmatics were significantly more likely to report heroin use (41.3% vs 12.5%; p = 0.006) and had a significantly higher prevalence of UDS results positive for opiates (60% vs 7%; p = 0.001) compared to subjects with DKA. The rates of cocaine use by history and UDS results did not differ significantly between the two groups.**

Conclusions: **At least since 1997, heroin insufflation is a common asthma trigger in this inner-city ICU and should be considered in the care of patients with life-threatening asthma.**

(CHEST 2003; 123:510–517)

Key words: asthma; cocaine; heroin; substance abuse

Abbreviations: DKA = diabetic ketoacidosis; ED = emergency department; UDS = urine drug screen

During much of the 1990s, heroin use in the United States rose steadily.[1] The current epidemic is characterized by new, young users, who increasingly report insufflation ("snorting"), rather than injection, as their sole method of use. In Chicago, New York City, Newark, and Detroit, insufflation is the most commonly reported means of heroin administration for those entering drug treatment programs. This shift toward insufflation has occurred in association with an increasing availability of heroin of higher purity.[2]

There are few previous reports of asthma associated with injection of heroin[3] and inhalation of morphine[4,5] or heroin.[6–8] Hughes and Caverly[7] described three patients requiring mechanical ventilation after inhaling heroin, one of whom "commonly developed wheezing within minutes or hours" of use. In the context of the current heroin epidemic, five patients with status asthmaticus associated with heroin inhalation (four from insufflation, one from smoking) were recently reported in Chicago.[9] These cases were characterized by preexisting asthma, the sudden onset of symptoms, relatively prolonged intubation, and eosinophilia.

During the fall of 1998, several patients admitted to the medical ICU at Cook County Hospital for severe asthma exacerbations reported that their

*From the Divisions of Occupational Medicine (Drs. Krantz and Hryhorczuk) and Critical Care (Dr. Franklin), Cook County Hospital; and Division of Epidemiology and Biostatistics (Dr. Hershow, Mr. Prachand and Ms. Hayden), University of Illinois School of Public Health, Chicago, IL.

Manuscript received July 26, 2001; revision accepted June 6, 2002.

Correspondence to: Anne Krantz, MD, MPH, Division of Occupational Medicine, Cook County Hospital, 1900 W Polk, Room 500, Chicago, IL 60612; e-mail: akrantz@uic.edu

asthma symptoms were triggered or exacerbated by heroin insufflation. Because of the apparent frequency of heroin-associated asthma in our ICU, and the relevance to patient care of identifying this trigger, clinical toxicology consultations have been requested routinely since December 1998 for all patients admitted to the ICU for asthma. These consults assess the contribution of recreational drug use to the patients' asthma, based on detailed histories.

The recognition of asthma associated with heroin insufflation at the end of 1998 raised the possibility that this was a novel phenomenon related to specific characteristics of heroin in use at the time. Thus, a 2-year retrospective chart review was undertaken to determine if this association was truly novel, or instead was the first recognition of an already established phenomenon. To further explore whether heroin use might be causally linked to severe asthma (as opposed to a confounding association related to delayed health-seeking behavior, nonadherence to medications, or limited access to health care), a retrospective case-control design was used to compare the rate of reported heroin use in ICU patients with asthma with that of patients with diabetic ketoacidosis (DKA) admitted to the ICU during the same 2-year period. Although clearly disparate illnesses, both DKA and severe, life-threatening asthma stem from chronic diseases that commonly affect younger adults and require close daily attention to self care. This report describes the epidemiologic and clinical characteristics of heroin-associated symptoms in asthmatics requiring ICU admission in this inner-city hospital, based on the detailed drug histories collected through routine clinical consultations, and the retrospective review, including the comparison of rates of drug use between asthmatic patients and patients with DKA.

Materials and Methods

Cook County Hospital is a public hospital that serves metropolitan Chicago. Approximately 11,000 adult patients per year are treated in the emergency department (ED) for asthma exacerbation, and roughly 4% require hospital admission for > 23 h. Patients requiring ICU admission represent roughly 10% of total asthma hospital admissions; the majority of these are admitted directly from the ED. Patients admitted to the ICU for asthma have either impending or actual respiratory failure, or a severe exacerbation with poor response to initial therapy.

Study 1: Case Series

The case series included all patients aged ≤ 50 years admitted to the ICU with a primary diagnosis of asthma exacerbation from January 1, 1999, through June 30, 1999. In all cases, the diagnosis was a clinical diagnosis made by the board-certified pulmonary/critical care physician caring for the patient. Patients with other causes of wheezing (*eg*, congestive heart failure, upper airway obstruction) were not included. These patients' charts were retrospectively reviewed. The report of the first chest radiograph performed during the hospital admission was also reviewed. Most of the patients had routine clinical toxicology consultations, performed by one physician (A.J.K.), which generally addressed patient histories regarding the following: clinical course of asthma, previous treatment, usual triggers, drug-use history, and the perceived relationship, if any, between drug use and asthma symptoms. Based on these detailed histories, specifically whether the patient attributed symptom exacerbation to discreet episodes of specific drug use, a clinical impression regarding heroin as an asthma trigger was formed, and a case series of patients with heroin-associated asthma symptoms was thus assembled. Four patients admitted to the ICU during the study period did not have formal toxicology consultations; these patients were included in the study.

Study 2: Retrospective Case-Control Study

Admissions to the ICU for the primary diagnosis of asthma from January 1, 1997, through December 31, 1998 were identified using admission logs maintained by the ICU director (C.F.). As above, the diagnosis was a clinical diagnosis made by the board-certified pulmonary/critical care physician caring for the patient. Patients with other causes of wheezing (*eg*, congestive heart failure, upper airway obstruction) were not included. All ICU admissions for patients aged 16 to 50 years were eligible for review. Patients > 50 years old were excluded to reduce the likelihood of including cases of COPD misdiagnosed as asthma. Patients whose charts could not be retrieved from medical records were excluded. Information abstracted from the medical records included the following: patient demographics and ICU admission date; age of asthma onset; intubation during the ICU admission; history of cigarette smoking; history of heroin and cocaine use; the relationship between drug use and this or other asthma attacks, if noted; and urine drug screen (UDS) results for drugs of abuse, if performed. The report of the first chest radiograph performed during the ICU admission was also reviewed.

The recording of drug use histories in the typical clinical setting is generally variable and incomplete, often with only pertinent positive findings being recorded. For the purpose of this study, an entry such as "social history: no drugs" was considered the same as "no heroin, no cocaine." If the use of one drug but not the other was recorded, a history of the use of the unrecorded drug was considered negative.

The opiate portion of the UDS in this hospital (Emit II Opiates 300/2000 Assay; Syva Company; Cupertina, CA) is an enzyme immunoassay that detects morphine in the urine. A positive screen result indicates exposure to morphine, diacetylmorphine (heroin), codeine, pharmaceutical opioids structurally related to morphine, or very high concentrations of meperidine and nalorphine. From January 1997 through February 1999, the cutoff for a positive test result was 300 ng/mL; a positive test result, if it reflected heroin use, would generally indicate use within the previous 50 h. In March 1999, the cutoff was increased to 2000 ng/mL; a positive test result, if resulting from heroin use, would generally indicate use within the previous 24 h.[10] This change in cutoff would in general lower the number of heroin users identified by this method; however, the change occurred during the course of study 1, which relied primarily on detailed history rather than UDS results, and thus was not believed to be an important limitation in this study.

Asthmatics undergoing intubation are sometimes administered morphine sulfate. For all patients with a positive UDS result for opiates, the date and time of the urine specimen collection was

noted. The physician orders and medication records were examined to determine the date and time that opiates (morphine sulfate, codeine, or other agent) were administered therapeutically in relation to the time of the specimen collection. If there was no evidence of prior opiate administration, a positive opiate screen result was assumed to reflect heroin use.

The cocaine portion of the UDS in this hospital (Emit II Cocaine Metabolite Assay; Syva Company) is an enzyme immunoassay that detects the cocaine metabolite benzoylecgonine at or above 300 ng/mL. Positive results for structurally unrelated compounds have not been observed.[11] A positive test result would generally indicate cocaine use up to 48 to 72 h prior.[12]

The charts of patients admitted to the ICU during the same time period with a diagnosis of DKA were reviewed. Patients with DKA who also had asthma were excluded. Data abstracted included patient demographics, cigarette and drug-use history, and results of urine drug screens, if performed. Demographic characteristics, rates of reported drug use, and UDS results among asthmatics were compared to those of patients with DKA. Student t test was used for comparisons of means, and χ^2 or the Fisher exact test were used for comparisons of proportions. Both studies were approved by the hospital institutional review board.

Results

Study 1: Case Series

In the first 6 months of 1999, there were 26 admissions for asthma in patients aged 16 to 50 years admitted to the ICU (Table 1). Three patients had two ICU admissions; thus, there were a total of 23

Table 1—*Selected Characteristics, History of Drug Use, and Effect of Heroin on Asthma Symptoms for 23 Patients**

Patient No.	Age, yr/Sex	Cocaine Use	Asthma Onset	Intubated	Effect of Heroin on Patients With Asthma
Group A: self-reported heroin use†, which triggers asthma					
1	26/male	No	Childhood§	No	Usually gets increased symptoms the morning after heroin use
2‡	29/female	Yes	Childhood	No/yes	Insufflates heroin daily and routinely gets chest symptoms 2 to 3 min after use, usually gets relief from MDI
3	30/female	No	Childhood	Yes	Insufflates heroin over 1 h, leads to symptom exacerbation, usually relieved by MDI use, this time continued to worsen over 2 days
4‡	32/female	Yes	Childhood	No/yes	Heroin cut with vitamin B_{12} precipitates wheezing within 5 to 10 min, partial relief with MDI (on methadone maintenance, both admissions)
5	30/male	No	Childhood	Yes	Heroin use causes wheezing occasionally, 1 h after use, especially if cut with diphenhydramine
6	35/male	Yes	Childhood	Yes	SOB after sniffing heroin; heroin-induced bronchospasm‖
7	32/male	No	Adult§¶	Yes	30 to 60 min after heroin use has symptom exacerbation usually relieved by MDI; this time got progressively worse over 2 days
8	31/male	No	Adult§¶	No	Shortness of breath and wheeze within minutes after finishing heroin use, usually relieved by MDI
9	42/male	Yes	Adult¶	No	Symptoms worse on mornings after heroin use the night before
10	28/female	Yes	Adult§	No	Symptom exacerbation after insufflating heroin approximately 50% of the time, relieved by MDI; never uses heroin without MDI "on hand"
11	29/male	Yes	Adult§	No	Heroin use worsens symptoms only when he also has a URI
12	40/male	Yes#	Adult§¶	Yes	Insufflated heroin daily until recently; precipitated symptoms infrequently, when cut with vitamin B_{12}
13	40/male	No	Adult§	Yes	Snorted heroin with SOB and wheezing‖
Group B: self-reported heroin use; heroin not reported as a trigger					
14	39/female	Yes	Not provided	Yes	Snorted heroin this morning‖
15	30/male	Yes	Childhood	No	Insufflates daily and has daily symptoms but heroin not experienced as a trigger; asthma well controlled during three long periods of abstinence
16	49/male	Yes	Adult§	No	Heroin use does not worsen symptoms
17	43/female	No	Adult§	Yes	Used heroin today‖
Group C: no reported recent or regular heroin use					
18	38/male	Yes	Childhood	Yes	
19	45/female	No	Childhood	No	
20	41/male	No	Childhood§	No	
21	28/male	Yes#	Adult§	No	
22	33/male	Yes#	Adult	Yes	
23‡	44/female	Possible**	Adult§	Yes/yes	

*MDI = metered-dose inhaler; SOB = shortness of breath; URI = upper respiratory tract infection.
†Excludes patients with history of single or remote use of heroin.
‡Patient had two ICU admissions, data reflects both admissions.
§Cigarette smoker.
‖Standardized interview not conducted; history quoted from chart.
¶Onset of heroin use predates onset of asthma diagnosis.
#Patient reports that cocaine use exacerbates asthma symptoms.
**History obtained from primary care physician.

patients. All patients were African American, except one patient who was white. The mean age of the patients was 35 years. Childhood onset of disease was reported by 45%. Fifteen of 22 patients (68.2%) reported using an inhaled corticosteroid. Of the 16 patients for whom the source of asthma care was recorded, 12 patients received their care in the ED as needed, and 4 patients through a continuity clinic. Of 23 chest radiograph reports available for review, 15 reports were read as having definite or possible abnormalities; the most common were localized pneumonic infiltrates (six patients) and hyperexpansion (three patients). One patient, a cocaine user, was reported to have possible fibrosis in a single lung field.

The 23 patients are listed in Table 1 and are separated into three groups: (1) group A members (patients 1 to 13) reported heroin use and stated that heroin insufflation was a trigger for asthma exacerbation; (2) group B members (patients 14 to 17) reported heroin use but did not attribute any asthma symptoms to it; and (3) group C members (patients 18 to 23) gave no history of use in the years preceding their admission (although two patients had a remote history of heroin use). Thus, there was a history of current or recent heroin use for 17 patients (groups A and B, Table 1).

All acknowledged heroin users reported insufflation as the sole method of use, except for one patient (patient 17), who had smoked it, and one patient who also had a remote history of injection. The duration of use reported for 10 patients ranged from 5 to 22 years. Nine patients reported daily use, and four patients reported less than daily use; the frequency of use was not reported in four cases. Of 14 UDS results interpretable for opiates, 10 results were positive, confirming recent use (all occurring in those patients with an acknowledged history of heroin use). Cutting agents identified by patients included vitamin B_{12} (five patients), a proprietary brand of diphenhydramine (three patients), and quinine (one patient). All patients identifying heroin cut with vitamin B_{12} said they were able to do so because of its brown color and unpleasant taste and smell.

Among the 17 acknowledged heroin users, 11 users described acute opiate withdrawal syndromes that included typical symptoms such as abdominal pain, diarrhea, and muscle aches. However, five patients also reported chest tightness or shortness of breath as part of their usual abstinence syndrome. These patients (four of whom also had heroin-triggered symptoms) generally reported that the respiratory symptoms would be partially relieved with use of a β-agonist spray, and completely relieved with the resumption of heroin insufflation. Five patients from groups A and B reported improved overall asthma control during sustained periods of abstinence.

In this group of 23 patients, 13 patients reported ever using cocaine. The methods reported were smoking crack (seven patients) and insufflation of cocaine powder (two patients). The frequency of cocaine use, reported for 10 patients, was less than once a week (seven patients), between one and six times per week (two patients), and daily (one patient). Of the 18 UDSs performed, 7 UDS results were positive for cocaine metabolite. Six of these seven patients had histories indicating cocaine use. Three of 13 acknowledged cocaine users reported that cocaine exacerbates their symptoms, and the others denied such an effect. This contrasts with the 13 of 17 heroin users reporting heroin-associated symptoms.

The small number of patients in this group with no history of heroin use makes meaningful comparisons between self-reported users and nonusers difficult. However, heroin users were less likely to report using an inhaled corticosteroid (10 of 17 patients vs 4 of 4 patients) and were more likely to be cigarette smokers (12 of 17 patients vs 1 of 4 patients) compared to nonusers. The proportion of adult-onset disease (9 of 16 patients vs 3 of 6 patients) and the intubation rate by ICU admission (10 of 19 patients vs 4 of 7 patients) were roughly equivalent between users and nonusers.

Patients With Heroin-Triggered Symptoms (Group A): Detailed descriptions of 13 patients reporting heroin as an asthma trigger (group A) are given in Table 1. Six of these patients specifically identified heroin as the sole or contributing cause of exacerbation that led to the current ICU admission. The time from insufflation to symptom exacerbation ranged from "immediate," within minutes, or within 1 h, to the following morning. The frequency with which using heroin precipitated symptoms was also variable, from "routinely" to "infrequently." Several patients reported that heroin only exacerbates symptoms when cut with specific agents (vitamin B_{12}, three patients; diphenhydramine, one patient), or when an upper respiratory tract infection was present (one patient). Typically, chest symptoms occurring after heroin insufflation were managed at home with a β-agonist spray.

Where detailed histories were available, no patients reported that heroin acted as a trigger from its first use; rather, it developed as a trigger following a period of at least several months, up to 7 years later. Five of the seven patients with adult-onset asthma in this series reported that the practice of heroin insufflation predated their history of asthma. One of

these patients (patient 10) reported that during the first 3 years of her asthma history, her chest symptoms were exclusively associated with using heroin, after which she acquired other common triggers. Other asthma triggers in this group included cold air, rainy weather, emotion upset, dust, upper respiratory tract infections, cigarette smoke, and occupational pesticide application.

Study 2: Retrospective Case Control Study

During the 2-year period studied, there were 106 admissions to the ICU for patients aged 16 to 50 years. Of these ICU admissions, 104 charts (98%) were available for review. These 104 ICU admissions represented 84 patients, with 9 patients having multiple ICU admissions. Selected demographic, clinical, and historical characteristics for the group of 84 patients are given in Table 2. Of 98 chest radiograph reports available for review for the 104 ICU admissions, 52 reports had definite or possible abnormalities. The most common abnormalities were hyperexpansion (n = 21) and localized pneumonic infiltrates (n = 13). "Possible interstitial lung disease" was reported for one patient, who had a history of smoking cocaine and insufflating heroin.

A history regarding drug use (any positive or negative information) was recorded by physicians for 92 ICU admissions (88.5%). All positive histories stated a specific drug or drugs. Using history alone, 53 patients were identified as using heroin only (n = 23), cocaine only (n = 15), or both drugs (n = 15). Where noted, insufflation was the predominant route for heroin exposure (19 insufflation, 6 smoking, 1 injection). UDS results were available for 63 ICU admissions (60.6%), of which 52 results were interpretable with regard to opiates. Opiates were detected in 34 UDS results (65.4%), and cocaine was detected in 22 UDS results (34.9%). These include 14 samples that were positive for both agents. Thus, despite the similar rates of self-reported heroin and cocaine use in general, the UDS revealed an almost twofold-greater prevalence of opiate use within the few days just prior to ICU admission. By combining history and positive UDS results, 60 patients were identified as users of heroin, cocaine, or both (Table 3). The majority of drug users in this group of ICU asthmatics were thus identified correctly identified by history alone.

Physician notes indicated 11 histories in which heroin was identified as a trigger for symptoms leading to the current ICU admission. There was no apparent temporal clustering of these ICU admissions, ICU admissions with positive heroin histories, or ICU admissions with positive UDS results positive for opiates.

During the study period, there were 46 DKA admissions to the ICU; these represented discrete patients, and all charts were available for review. Four patients who also had asthma were excluded.

Table 2—*Demographic and Clinical Characteristics for 84 Patients Admitted to ICU for Status Asthmaticus**

Characteristic	Total Sample (n = 84)
Age at admission, yr	
Mean†	33.4
≤ 18	1 (1)
19–29	33 (39)
30–39	27 (32)
40–49	22 (26)
≥ 50	1 (1)
Race/ethnicity	
White	1 (1)
Hispanic	10 (12)
Black	73 (87)
Other	0 (0)
Gender	
Male	46 (55)
Female	38 (45)
Cigarette smoking	
Yes	38 (55)
No	31 (45)
Missing	15
Asthma onset	
Childhood	35 (60)
Adult	23 (40)
Missing‡	24

*Data are presented as No. or No. (%). Percentages exclude missing data.

†For patients with multiple ICU admissions, age at first ICU admission.

‡No. unknown includes two patients with multiple ICU admissions where history was discrepant.

Table 3—*Drug-Use Characteristics for 104 Patient Admissions**

Characteristics	No. (%)
Drug history ascertained	
Yes	92 (89)
No	12 (11)
UDS performed	
Yes	63 (61)
No	41 (39)
Drug use identified by history or positive UDS result	
Total patients with drug use	60 (58)
Heroin only	27 (26)
Cocaine only	11 (10)
Both heroin and cocaine	22 (22)
No heroin or cocaine use identified	34 (33)
Unknown (no history or positive UDS result available)	10 (10)

*Percentages exclude missing data.

The demographic characteristics, drug-use histories, and UDS results in asthmatics were compared to those of the patients with DKA (Table 4). There was no significant difference in mean age or sex distribution between the groups, but the racial makeup of the two groups did differ ($p = 0.001$), with the DKA group having a higher percentage of Hispanics and non-Hispanic whites than the asthma group. Compared to the patients with DKA, asthmatics were significantly more likely to report heroin use (41.3% vs 12.5%; $p = 0.006$). Asthmatics were more likely to report cocaine use as well, but the difference was not statistically significant. Asthma patients were more likely to have a UDS performed (60% vs 36%; $p = 0.011$), and it was more likely to be positive for opiates (59.6% vs 7.0%; $p < 0.001$). There was no difference in the rate of cocaine detected on UDS between the groups.

Discussion

We have observed that heroin insufflation is a common trigger for asthma symptoms among patients requiring ICU admission for asthma in an urban public hospital. This phenomenon has occurred sporadically since March 1997 and may have been operative prior to that date. In the first 6 months of 1999, the majority of persons (13 of 23 patients) admitted with severe asthma to the ICU gave a clear history that heroin insufflation precipitated asthma exacerbations generally, and in some cases, clearly precipitated the symptoms that led to the ICU admission. Detailed histories suggest that heroin use frequently resulted in less severe symptoms that were managed at home. The high rate of UDS positivity for opiates confirms the history of recent use in many patients, and strengthens the temporal linkage between heroin use and severe symptoms. These temporal associations, coupled with the finding that heroin use was more commonly identified in ICU patients with asthma than in a comparison group with DKA, support a relationship between heroin insufflation and asthma.

Table 4—*Demographic and Clinical Characteristics for Patients Admitted to the ICU for Status Asthmaticus or DKA**

Characteristics	Asthma	DKA	p Value
By individual patient			
No.	84	42	
Male	46 (55)	27 (64)	0.502
Female	38 (45)	15 (36)	
Mean age, yr	33.4	32.1	0.23 ($t = -1.29$)
African American	73 (87)	26 (62)	< 0.001
Latino	10 (12)	9 (21)	
White	1 (1)	6 (14)	
Other	0 (0)	1 (2)	
By ICU admission			
No.	104	42	
Drug history ascertainment	92 (89)	40 (95)	0.351
History of heroin use	38 (41)	5 (12)	0.006
History of cocaine use	30 (33)	7 (17)	0.18
UDS performed	63 (60)	15 (36)	0.011
UDS result positive for opiates	34/52† (65)	1 (7)	< 0.001
UDS result positive for cocaine	22/63 (35)	4 (40)	0.76

*Data are presented as No. (%) or No.

†Denominator excludes 11 samples collected after morphine administration.

A conversation with a former user revealed that the process of heroin insufflation (snorting) involves using a razor to finely pulverize heroin powder, laying it in "lines" (approximately 1 cm^3 per line), and forcefully sniffing a total of three to four lines through a straw or rolled-up dollar bill, over a few minutes. The user then "throws" his or her head back and sniffs forcefully and repeatedly to make sure all the material is inhaled. Water or another drinking liquid is often dabbed into the nostril, to moisten the remaining powder, and keep it from falling out of the nose.

Several reports provide data suggesting possible mechanisms for heroin-related asthma. Chest tightness, wheeze, and rhinitis were reported in temporal relationship to morphine dust exposure in two pharmaceutical employees[4,5] and to heroin exposure in a drug dealer.[6] A bronchoprovocation test result, performed on the dealer with extracts of pure heroin, was positive, as was a skin-prick test result. In one of the pharmaceutical workers, both inhalational and nasal challenge with morphine resulted in a decline in the patient's pulmonary function, associated with dyspnea, wheeze, sneezing, and rhinorrhea.[5] Nasal lavage after each challenge demonstrated an influx of basophils and eosinophils in an allergic pattern. Thus, these data suggest that uncontaminated morphine and heroin produce bronchospasm, possibly through an allergic mechanism.

Pulmonary mast cell degranulation may be another possible mechanisms for heroin-induced bronchospasm. Intradermal and IV morphine and synthetic opioid administration stimulate histamine release from mast cells through a direct pharmacologic mechanism, independent of an opiate receptor.[13,14] Histamine release occurs in one fifth of patients receiving postoperative IV analgesia with morphine or heroin.[15] Edston and von Hage-Hamsten[16] observed that β-tryptase, a mast cell protease, was elevated in cases of sudden death in heroin users compared to those dying suddenly of known, nonimmunologic causes. Another mecha-

nism may relate to opioid inhibition of cholinesterases, which has been demonstrated in animal species[17]; the clinical significance of this in humans is unknown. Yet another possibility is that heroin powder, its contaminants, and/or cutting agents may serve as nonspecific airway irritants.

Several features of our data provide further insight into the mechanisms of heroin-associated asthma symptoms. The lack of temporal clustering of ICU admissions with heroin use or heroin-associated symptoms argues against the role of a specific heroin "batch," but rather suggests an endemic phenomenon. The histories given by our patients with heroin-associated symptoms differ with regard to the consistency with which heroin use produces chest symptoms, the time lag from an episode of use to symptom exacerbation, and other characteristic features (presence of upper respiratory tract infection, specific cutting agents). This suggests that variations in the degree of underlying airway hyperreactivity may play a role, but also that there may be different mechanisms involved in different patients. No patients, however, reported that heroin was a trigger from the time of first use, suggesting that a pharmacologic effect alone involving mast cell degranulation is unlikely, though perhaps it becomes clinically important in combination with (and contributes to) a sufficient level of underlying airway inflammation. The invariable reporting of a latency period would be consistent with allergic sensitization.

In contrast to the nonreceptor-mediated mechanisms noted above, potential receptor-mediated effects of opiates might be expected to reduce bronchospasm by reducing airway cholinergic tone. An opiate receptor has been localized in the rat airway,[18] and in isolated human airways, a μ-opioid agonist inhibits cholinergic neurotransmission by a mechanism involving the opiate receptor.[19] In mild asthmatics, IV morphine inhibits the cholinergic component of bronchoconstriction induced by water[20] and sulfur dioxide.[21] In fact, the theoretical potential for peripherally acting opioids for therapeutic use in asthma has been suggested.[19] These receptor-mediated effects, if indeed clinically relevant, are perhaps being overridden by other mechanisms mentioned above, which, given the frequent high doses of heroin used, physical form and route of exposure (dust inhalation), and presence of adulterants, may result in the predominant picture of bronchospasm that our patients reported.

Opiate receptor-mediated effects may, however, be relevant to the seemingly paradoxical report of chest tightness and wheeze during acute heroin withdrawal. Five of the 11 patients who had heroin withdrawal reported chest symptoms in addition to other typical abstinence symptoms. Chest symptoms have not, to our knowledge, been previously reported as features of opiate withdrawal.

Both central and peripheral cholinergic mechanisms appear to be involved in the expression of opiate withdrawal.[22] Perhaps bronchospasm results from centrally mediated increased vagal tone during opiate withdrawal, and is manifest as wheezing in those with asthma. Alternatively, if adaptation to receptor-mediated effects occurs in the airways in opiate dependence, then withdrawal might result in a peripheral rebound in cholinergic tone, again resulting in bronchospasm in those with underlying asthma. While these mechanisms are speculative, the clinical observation underscores the importance of adequately treating opiate withdrawal in the setting of a severe asthma exacerbation.

As revealed by interview and UDS results, heroin was more commonly associated with ICU asthma than cocaine. By contrast, the prevalence of cocaine and opiate use by UDS in patients presenting for asthma treatment to an ED in Philadelphia was found to be 13% and 5.8%, respectively (although 23% of eligible patients declined participation).[23] In Chicago, multiple indicators of drug use suggest that cocaine is used more frequently than heroin.[24] Inhaled alkaloidal cocaine ("crack") produces an increase in airway resistance,[25] and wheezing is common in some published series of cocaine smokers.[26] The disproportionate representation of heroin use in our patients with severe asthma may be due to greater potency of heroin as an asthma trigger or to more common use of heroin in patients who utilize Cook County Hospital. Alternatively, it is possible that opiate intoxication is more likely than cocaine to impair the asthmatic patient's perception of dyspnea, resulting in delayed clinical presentation and progression to more severe acute exacerbation. Concurrent cocaine use was fairly common in patients who used heroin, so it is also possible that cocaine may have been a co-trigger of asthma symptoms in that subgroup. These possibilities may be clarified by further exploration of the association of drug use with less severe asthma, and of the linkage between drug use and asthma in other medical centers.

There are several potential limitations to this study. Data from the 2-year review of ICU admissions are based on retrospectively abstracted medical records and depend on the accuracy and completeness of histories constructed by a diverse group of clinicians. Given the substantial rate of acknowledged drug use in both patient groups, it is unlikely that patient underreporting is significant. It is possible, however, that our finding that heroin use was more common in asthmatics than in patients with DKA stems from more intense clinician screening for drug use in the former group, rather than a true

difference in exposure. It is plausible that clinicians considered inhalational exposures, including drug use, a potential asthma trigger, and probed more intensely for it through interview or UDSs. Indeed, the UDS was performed more frequently in asthmatics (60% vs 36%). It is reassuring that ascertainment of any drug-use history was roughly equivalent among asthmatics and patients with DKA as reflected by the medical history (89% vs 95%, respectively). Thus, the observed disparity in the ordering of UDSs between asthmatics and patients with DKA may simply reflect the difference in clinical suspicion arising from the histories in the two groups. Nevertheless, a potential bias cannot be ruled out in the case-control portion of the study.

The control of factors contributing to asthma severity is a critical component of asthma care.[27] The recognition that heroin insufflation is a common trigger in inner-city patients with life-threatening asthma adds this practice to the list of potential triggers for which asthmatics should be queried. Its proper identification allows clinicians the opportunity to offer specific treatment (drug rehabilitation), without which asthma education and self-management techniques will be unsuccessful. The contribution of heroin insufflation to less severe asthma, the mechanism(s) of heroin-induced bronchospasm, and the optimal approaches to the treatment of opiate addiction in asthmatics are all relevant areas for further investigation.

ACKNOWLEDGMENTS: We thank Drs. David Gummin and Paul Bonucci for assistance in data collection, Drs. Henri Frischer and Jay Shannon for review of the manuscript, and Dr. Lawrence Ouellet and the staff of the Community Outreach Intervention Projects for information provided on drug use practices in Chicago.

References

1 NIDA Research Report: Heroin abuse and addiction. Bethesda, MD: National Institutes of Health, National Institute on Drug Abuse, 1997; publication No. 00–4165
2 Community Epidemiologic Work Group. Epidemiologic trends in drug abuse: Volume I, Epidemiologic trends in drug abuse. Rockville, MD: National Institute on Drug Abuse, 1999; publication No. 00–4529
3 Ghodse AH, Myles JS. Asthma in opiate addicts. J Psychosom Res 1987; 31:41–44
4 Agius R. Opiate inhalation and occupational asthma [letter]. BMJ 1989; 298:323
5 Ulinski S, Placzynski C, Gorski P. Occupational rhinitis and bronchial asthma due to morphine: evidence from inhalational and nasal challenges. Allergy 1996; 51:914–918
6 Shaikh WA. Allergy to heroin. Allergy 1990; 45:555–556
7 Hughes S, Caverly PMA. Heroin inhalation and asthma. BMJ 1988; 297:1511–1512
8 Merigan K, Blaho K. The role of pharmacology and forensics in the death of an asthmatic. J Anal Toxicol 1995; 19:522–528
9 Cygan J, Trunsky M, Corbridge T. Inhaled heroin-induced status asthmaticus: five cases and a review of the literature. Chest 2000; 177:272–275
10 Cone EJ, Jufer R, Darwin WD, et al. Forensic drug testing for opiates VII: urinary excretion profile for intranasal (snorted) heroin. J Anal Toxicol 1995; 20:379–392
11 Emit II Cocaine Metabolite Assay [package insert]. Cupertina, CA: Syva Company, 2001
12 Baselt RC, Cravey RH. Disposition of toxic drugs and chemicals in man. 4th ed. Foster City, CA: Chemical Toxicology Institute, 1995
13 Barke KE, Hough LB. Minireview: opiates, mast cells and histamine release. Life Sci 1993; 53:1391–1399
14 Deonicke A, Moss J, Lorenz W, et al. Intravenous morphine and nalbuphine increase histamine and catecholamine release without accompanying hemodynamic changes. Clin Pharmacol Ther 1995; 58:81–89
15 Witherington DE, Patrick JA, Reynolds F. Histamine release by morphine and diamorphine in man. Anaesthesia 1993; 43:26–29
16 Edston E, von Hage-Hamsten M. β-Tryptase measurements post-mortem in anaphylactic deaths and in controls. Forensic Sci Int 1998; 3:135–142
17 Galli A, Esterina R, Giannini L, et al. Reversible inhibition of cholinesterase by opioids: possible pharmacologic consequences. J Pharm Pharmacol 1996; 48:1164–1168
18 Tang J, Chou J, Zhang AZ, et al. Met^5-enkephalin-arg^6-phe^7 and its receptor in the lung. Life Sci 1983; 32:2371–2377
19 Belvisi MG, Stretton CD, Verleden GM, et al. Inhibition of cholinergic neurotransmission in human airways by opioids. J Appl Physiol 1992; 72:1096–1100
20 Eschenbacher WL, Bethel RA, Boushey HA, et al. Morphine sulfate inhibits bronchoconstriction in subjects with mild asthma whose responses are inhibited by atropine. Am Rev Respir Dis 1984; 130:363–367
21 Field PI, Simmul R, Bell SC, et al. Evidence for opioid modulation and generation of prostaglandins in sulfur dioxide (SO_2)-induced bronchoconstriction. Thorax 1996; 51:159–163
22 Sharif SI, El-Kadi AOS. The role of cholinergic systems in the expression of morphine withdrawal. Neurosci Res 1996; 25:155–160
23 Rome LA, Lippman ML, Dalsey WC, et al. Prevalence of cocaine use and its impact on asthma exacerbation in an urban population. Chest 2000; 117:1324–1329
24 NIDA. Proceedings of the Community Epidemiologic Work Group. Bethesda, MD: National Institute on Drug Abuse, April 2000
25 Tashkin DP, Kleerup EC, Koyal SN, et al. Acute effects of inhaled and IV cocaine on airway dynamics. Chest 1996; 110:904–910
26 Haim DY, Lippman ML, Goldberg SK, et al. The pulmonary complications of crack cocaine: a comprehensive review. Chest 1995; 107:233–240
27 National Asthma Education and Prevention Program. Expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health, 1997; publication No. 97–4051