Drug-induced pulmonary disease

Part II. Categories of drugs

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Drugs are capable of producing a variety of adverse pulmonary responses. *Part 2* deals with drugs classified by pharmacological action. A homogeneous type of reaction may be seen within a particular group of drugs. However, this section is primarily designed to provide a more accessible reference for such a large number of therapeutic agents.

Analgesics

Analgesic and anti-inflammatory drugs are included in the ASA triad and narcotic analgesics. Carbamazepine has already been discussed in *Part 1*. Narcotics produce a dose-dependent central respiratory depression. Most of the adverse pulmonary responses are caused by the illicit use of narcotic drugs and will be discussed under that section.

Overdoses of acetylsalicylic acid (ASA) can produce central respiratory stimulation and noncardiogenic pulmonary edema. Therapeutic serum levels are in the 10 to 20 mg/dl range. At levels of 35 mg/dl, respiratory alkalosis occurs. Severe hyperpnea is manifest at levels of 50 mg/dl.[1] At a serum level of 45 mg/dl (about 70 tablets), noncardiogenic pulmonary edema occurs.[2] The pulmonary capillary wedge pressure is normal and the chest roentgenogram takes 3 to 8 days to clear. Increased vascular

permeability, pulmonary lymph flow, and lymph protein clearance have been observed in experimental studies.[3]

The ASA triad is characterized by asthma, nasal polyposis, and drug sensitivity. It was initially described following the use of ASA, but other medications are also capable of producing this reaction (*Table 1*). The first manifestation of the syndrome is vasomotor rhinitis with a watery discharge. Typically this develops in the second or third decade in a nonatopic individual who had previously taken ASA with impunity. (Only the reference drug will be mentioned with the understanding that the other medications can also produce this response.) The reaction is at first intermittent, later perennial. It is followed by the appearance of nasal polyps and by mid-life, most patients will have an asthmatic response.[4]

The syndrome is not a hypersensitivity response despite the asthma and angioedema, which may be seen following absorption of these medications. Skin and immunologic tests are negative. Further, other forms of salicylic acid such as sodium salicylate are incapable of producing a response in the ASA-sensitive patient.[4] The mechanism of action is postulated to be an inhibition of prostaglandin (PG) synthetase and a disruption in the balance between naturally occurring bronchoconstrictor ($PGF_{2\alpha}$) and bronchodilator (PGE series) prostaglandins.[5] The usual response to this disruption is bronchoconstriction, but bronchodilation has also been reported.[6] Most of the drugs in *Table 1* have been shown to affect PG biosynthesis. Also, not all drugs capable of altering PG metabolism have been incriminated as inducers of the ASA triad. In those drugs that alter PG metabolism, the degree of bronchoconstriction has been shown to be proportional to the effect on PG biosynthesis. Thus, not all drugs listed in *Table 1* will produce a response in the ASA-sensitive patient and not all responses will be of the same severity. The minimum-inducing dosages are usually within the single dose range.[4, 5, 7, 8] Most of the drugs producing this response fall into the broader category of anti-inflammatory, nonsteroidal analgesics, and it is for this reason that the ASA triad has been called analgesic asthma by some authors.

Table 1. ASA triad

Acetylsalicylic acid
Antipyrine
Dextropropoxyphene
Fenoprofen
Flufenamic acid
Ibuprofen
Indomethacin
Mefenamic acid
Naproxen
Parcetamol
Phenylbutazone
Tartrazine (FD & C no. 5)

The frequency of the syndrome in asthmatics is approximately 4%.[7, 9, 10] The male to female ratio varies between series. Patients may or may not be atopic, 3% versus an expected 10% in one series.[2] Family studies reveal rare clusterings. One report[11] described two sisters with the syndrome and another[12] claimed an autosomal recessive mode of inheritance.

Symptoms of bronchial constriction are either acute (a few to 20 minutes after ingestion) or are delayed (approximately 2 hours). Other symptoms include urticaria and angioedema; hypotension, which may lead to a loss of consciousness; nausea; vomiting; intestinal cramps; diarrhea; cyanosis; and a flush to the upper part of the body. Concurrent infection may precipitate or worsen the severity of the attack.[13]

Treatment starts with avoidance of the offending drug. Beta adrenergic agonists will reverse the airway response. Corticosteroids will diminish the recovery time, but even pretreatment will not prevent the response. Nasal polypectomy is reserved for symptoms of nasal obstruction only; it will not alter the response to ASA and the polyps usually recur.[13]

Tartrazine (FD & C yellow dye No. 5) is not an analgesic nor is it known to affect PG biosynthesis. However, it can provoke symptoms of the ASA triad in a small number of ASA-sensitive patients. As a dye, it is contained in a number of medications.[14]

Antibiotics (*Table 2*)

Aminoglycoside antibiotics, polymyxins, and viomycin have already been discussed in the section on respiratory depression. Griseofulvin, isoniazid, para-aminosalicylic acid, penicillin, streptomycin, sulfonamides, and tetracycline are capable of producing a drug-induced SLE syndrome (*Part I*). In addition, isoniazid has been reported to cause a hypersensitivity-like pneumonitis with peripheral eosinophilia.[15] Penicillin has also been reported to cause a hypersensitivity pneumonitis distinct from systemic anaphylaxis with peripheral eosinophilia (as high as 80%), alveolar infiltrates, pleural effusions, and positive skin tests.[16]

Sulfonamides have been reported to cause a true Loeffler's syndrome with fever, cough, dyspnea, and migratory infiltrates with peripheral eosinophilia.[17] A hypersensitivity pulmonary response has also been reported following the use of a sulfonamide-containing vaginal cream.[18]

Para-aminosalicylic acid is estimated to produce a hypersensitivity-like response in approximately 0.3% to 5.0% of patients receiving the medication.[19] The patient is usually nonatopic and the syndrome is observed more commonly when large doses are used initially rather than gradually increasing the dosage. Common adverse reactions include fever (to 105 F), rash, malaise, headache, dry cough, eosinophilia, alveolar infiltrates, and lymphadenopathy. Pleural effusion and hepatomegaly have been observed.[19, 20] The symptoms usually start during the third week of treatment and gradually disappear 2 to 3 weeks after withdrawal of the drug. Cases of angioneurotic edema with laryngeal edema, coughing, and wheezing have also been reported.[20]

Except for corticosteroids, nitrofurantoin is the drug most often reported as causing an adverse pulmonary reaction.[21] To gain an appreciation of the relative risk, the manufacturer collected data over a 16-year period. During that time, 237 adverse pleuropulmonary reactions were reported during an estimated 44 million courses of the drug.[22] Reactions due to nitrofurantoin are divided into acute or chronic with no

Table 2. Antibiotics capable of producing adverse pulmonary responses

Antibiotics
Gentamicin
Isoniazid
Kanamycin
Neomycin
Nitrofurantoin
Para-aminosalicylic acid
Penicillin
Streptomycin
Sulfonamides
Tetracycline
Tobramycin
Viomycin
Antifungals
Colistin
Griseofulvin
Polymyxin B

definite relationship between the two groups, although both can be fatal.[23]

Lymphopenia occurs with the acute reaction with a decrease in both the B- and T-cell population. The lymphocyte transformation test against nitrofurantoin need not be positive for a patient to experience an adverse reaction.[23] The acute reactions and guide to incidence are acute asthma (rare), acute tracheobronchitis with a normal chest roentgenogram (very rare), pleural effusions (usually in association with hypersensitivity pneumonitis), and hypersensitivity pneumonitis (the most frequent response).[22, 24, 25]

The onset of symptoms due to hypersensitivity pneumonitis is usually within 2 hours to 10 days after starting the medication, although symptoms have begun as late as one year.[26, 27] Usually the patient will have fever, chills, dyspnea, and cough. This reaction occurs much more quickly on subsequent uses of the drug. Findings at physical examination are often suggestive of more diffuse involvement than that seen on the chest roentgenogram. Pleuritic pain and pleural rubs may be present. Subacute reactions with milder symptoms have also been documented.[27]

The chest roentgenogram reveals diffuse alveolar or alveolar-interstitial infiltrates. Pleural effusions and varying degrees of peripheral eosinophilia may be present,[22] as well as eosinophils in the sputum (unpublished data).

Treatment is based on discontinuance and avoidance of the drug. Corticosteroids and antihistamines provide symptomatic relief. The infiltrates clear spontaneously within a 24- to 48-hour period; one author suggested that another cause be sought if the infiltrates do not clear during this time.[21]

Chronic reactions occur less commonly and are estimated at 3% of all pleuropulmonary reactions to nitrofurantoin.[22] There is no relationship to the acute response; deaths are more frequently encountered in this group. There are two patterns of response: interstitial fibrosis and desquamative interstitial pneumonitis.

Interstitial fibrosis starts insidiously after 6 months to 6 years of therapy. Symptoms are cough and dyspnea; there is no fever, eosinophilia, or pleural effusion.[22, 26] Desquamative interstitial pneumonitis (DIP) was described in three patients who had received the drug for 2 to 5 years.[28] In contrast to the interstitial fibrosis, which shows only a variable response to corticosteroid therapy, there was good reversibility with treatment. Physical and roentgenologic examinations were similar. Histologically, the DIP response showed IgE and Ce deposits in the interstitial cells in one patient.[28]

Endocrinologic agents (*Table 3*)

Chlorpropamide has been described as causing a hypersensitivity pneumonitis. Vitamin D can produce pulmonary calcification and propylthiouracil can cause a drug-induced SLE syndrome. Corticosteroids are discussed in *Part 3*. Prostaglandins may elicit a bronchoconstrictive response; these are occasionally used to induce labor for either

Table 3. Endocrinologic agents capable of producing adverse pulmonary responses

Hormonal agents
Corticosteroids
Estrogens
Pituitary snuff
Prostaglandins
Vitamin D
Therapeutics
Chlorpropamide
Propylthiouracil

delivery or abortion and the response can be seen following the intramuscular, intravenous, or intra-amniotic route of administration. The effect on the bronchial smooth muscle is physiologic and problems may be encountered, especially in the asthmatic patient.[29]

Estrogens may produce an adverse pulmonary reaction through a number of mechanisms: by producing a pulmonary embolus, by causing a drug-induced SLE syndrome, or by causing pulmonary hypertension (*Part I*). It has been estimated that the risk of thromboembolic disease in age-matched patients taking oral contraceptives was increased by a factor of 5 to 11 (or from 5 to 47/100,000).[30] The mortality risk from pulmonary embolus is increased by a factor of 7 or 8 (or from less than one to approximately three patients per 100,000).[31] Some associated variables that increase the risk for the patient taking oral contraceptives include obesity,[30] age,[31] and prolonged bedrest.[32, 33] The estrogen content of the oral contraceptives is directly proportional to the thrombogenic risk.[34]

Pituitary snuff can produce an acute bronchospastic reaction, which occurs within minutes of inhalation. Some particles in the snuff are smaller than 5 μ and, therefore, probably reach the alveolar level.[35, 36] A less common response is a hypersensitivity pneumonitis. The allergen is presumed to be the bovine or porcine proteins contained in the preparation.[36] Typical symptoms include increasing dyspnea, lethargy, decreased exercise tolerance, and mild fever. Physical examination reveals tachypnea and occasionally medium rales over the middle and lower lobes. Pulmonary function tests (PFT) show a decreased diffusing capacity, compliance, vital capacity, and arterial saturation of oxygen. The chest roentgenogram shows a miliary pattern of diffuse ground glass appearance. Eosinophilia is present.[35]

Treatment is discontinuance of the use of the drug and corticosteroids. This inflammatory response can progress to interstitial fibrosis if the drug is continued.[36] Synthetic lysine vasopressin may be substituted for the animal-derived preparation. One instance of a hypersensitivity reaction from this preparation was reported to be similar to that of the animal-derived drug.[36] However, no PFTs were reported and the symptoms may have been nonspecific. A similar case was subsequently reported; the patient tolerated the synthetic preparation with no change in the PFTs.[37] Alternatively, an injectable or coarser-grain preparation may be used.[35, 36]

Miscellaneous

Clonazepam has been reported to produce bronchial hypersecretion in a few patients and can cause respiratory difficulties in infants.[38] A paradoxical asthmatic reaction to inhaled isoproterenol in atopic patients has been reported. This reaction was not related to the propellant.[39]

Sodium cromoglycate has been associated with a hypersensitivity-like response with fever, eosinophilia, and pulmonary infiltrates.[40] A patient was described who demonstrated granulomatous inflammation of the pulmonary blood vessels, bronchial walls, and interstitium on pulmonary histopathology. With chronic use, there was a gradual onset of sputum production, fever, a burning sensation in the chest, and weight loss. The chest roentgenogram showed diffuse interstitial infiltrates. There was a decrease in the FEV_1 and a 10% eosinophilia. The patient was placed on a regimen of corticosteroids and, after 6 months, the chest roentgen-

ogram, PFT abnormalities, and symptoms cleared.[41]

A case of hypersensitivity pneumonitis was described in a patient on his 24th day of treatment with diphenylhydantoin. Presenting signs included a fever and macular rash. There was eosinophilia, hypoxemia (the PaO_2 was 59 torr on room air), diffuse miliary infiltrates on the chest roentgenogram, and granulomatous hepatitis. By the 50th day after withdrawal of the drug, all physical and biochemical signs of toxicity had disappeared.[42]

In the late 1950s a controversy developed concerning interstitial fibrosis as a manifestation of chronic use of diphenylhydantoin. Abnormal chest roentgenograms showing increased bronchovascular markings resembling interstitial fibrosis were seen in 98% of patients taking medication for 2 to 12 years.[43] A similar study found no instance of abnormal chest roentgenograms.[44] Results of another study showed changes in the PFTs with chronic use of the drug; 45% had a decreased D_LCO and 50% had either an increased $A\text{-}aO_2$ gradient or did not increase their D_LCO with exercise. These changes were independently related to macrocytosis and were more common if the patient had started therapy before 8 years of age.[45] This was refuted by the findings of a study of 43 patients who had taken diphenylhydantoin for at least 2 years. Physical examination, chest roentgenogram, and vital capacity were normal unless an independent abnormality was present, e.g., chest wall deformity.[46] The controversy remains unresolved.

Interstitial pneumonitis has been described with chronic administration of gold salts. This response was seen in two patients after total doses of 325 and 420 mg. Symptoms included fever, cough, dyspnea, and rash. The chest roentgenogram showed interstitial or mixed infiltrates which, on histology, revealed lymphocytes and plasmocytes in the alveolar septa with interstitial fibrosis. Treatment consisted of discontinuance of the gold and administration of corticosteroids.[47] The presenting symptom of gold bronchitis, a dry cough, is a poorly documented, but widely recognized entity according to Rosenow,[48] indeed, no documentation could be found. Gold is also capable of producing a drug-induced SLE syndrome.[49]

Iodides are capable of eliciting many varied pulmonary responses. Potassium iodide can produce hilar and mediastinal lymphadenopathy (*Part I*). Iodinated oils used in testing procedures and radioactive iodine are discussed below. Iodism, or chronic iodide poisoning, may be associated with a productive cough or pulmonary edema. Both entities clear with discontinuance of the drug.[50]

Pleural thickening is the most common pleuropulmonary side effect due to chronic methysergide use. This has a ground glass appearance on chest roentgenogram and can clear spontaneously with cessation of the drug.[21] A pleural effusion may be seen. It may present as an acute process with pleuritic pain and a rub, or the onset may be more insidious. The effusion may be unilateral or bilateral. Pulmonary fibrosis has also been seen with the chronic use of methysergide. There is a slow onset over 6 months to 6 years with cough and dyspnea. It may be diffuse or can present as localized areas of pleuropulmonary fibrosis resembling a mass lesion. Fibrosis may reverse upon discontinuance of the drug.[12, 51]

A variety of inflammatory patterns have been seen following mineral oil abuse including: pneumonitides, bron-

chitis, bronchiolitis, granulomas, fibrosis, atelectasis, or symptoms of asthma. All of these responses may be acute (except the fibrosis) or chronic, diffuse or localized. PFTs show a mixed picture of air flow obstruction and hyperinflation. More than 50% of affected patients are asymptomatic and are discovered by abnormal chest roentgenograms or at autopsy. Treatment consists of patient education and the use of corticosteroids in severe cases.[21, 52] Oil granulomas can coexist with carcinomas. A case was reported of a patient who had abused the use of oil drops for 10 years before his death from alveolar cell carcinoma. Animal models have suggested a carcinogenic potential resulting from chronic mineral oil abuse.[52, 53]

Penicillamine has been implicated in the pathogenesis of Goodpasture's syndrome in three patients. All had Wilson's disease and had been treated for 2 to 3½ years. Presenting symptoms were hemoptysis and respiratory failure; there were no premonitory signs. Chest roentgenograms showed diffuse infiltrates. It was estimated that this entity would occur in less than 0.5% of all patients treated with the drug.[54] A case of hypersensitivity pneumonitis with an insidious onset has also been described. All signs, symptoms, and abnormal tests had reverted to normal 3 months after use of the drug was discontinued.[55] A possible role of penicillamine in the development of bronchiolitis obliterans has been reported by one author.[56]

Drugs used as investigational aids

Fluorescein, used in retinography, has been reported to be a cause of noncardiogenic pulmonary edema.[57]

Bronchography, when performed with iodinated oils such as Lipiodol or Ethiodol, may cause pulmonary problems as a reflection of a substance other than air occupying the air passages. The most severe abnormalities of acute hypoxemia and restrictive ventilatory defects occur in patients with preexisting lung disease. In one study of patients with coal workers' pneumoconiosis undergoing bronchography with Lipiodol, the changes in the arterial blood gases were: PaO_2, 75 to 56 torr; SaO_2, 93.5% to 85%; $PaCO_2$, 42.4 to 56.5 torr; A-aO_2, 16 to 30 torr; and pH, 7.45 to 7.38. In unilateral bronchography, the vital capacity (VC) decreased by 20% and the maximal breathing capacity (MBC) also decreased by 20%; in bilateral bronchography, the VC decreased by 33% and the MBC by 31%. These changes returned to baseline by 3 hours.[58]

There is a high incidence of adverse pulmonary reactions following lymphangiography. Two cases of pulmonary edema occurring within 5 hours of injection in patients who had received recent pulmonary radiation have been reported.[59] A case of intrapulmonary hemorrhage with associated anemia has also been described.[60] However, in contrast to these unusual reactions, it has been estimated that approximately 50% of all patients undergoing lymphangiography will have an oil embolus with the intensity of symptoms being closely related to the premorbid state of the lungs. These emboli can, on occasion, produce pulmonary infarction. The same type of reaction is seen with the use of oily contrast media for hysterosalpingography, myelography, urethrography, and hepatolienography (in hysterosalpingography, an embolus is usually seen only when the pelvic veins are observed to be filling with the medium).[21, 61, 62] Pulmonary complications are a reflection of both the rapidity of injection and the volume of injected material. Emboli are felt to be unlikely with a total dose less than 0.15 ml/kg

body weight, when given at a rate of 1 ml/8 min.[21] The incidence of emboli appears related not to the underlying pathology, but to the presence or absence of lymphatic obstruction.[62]

The most consistent change in the PFTs is in the diffusing capacity. The results of one study suggest a universal decrease, even in asymptomatic patients;[63] the results of another study document persistent reductions in two thirds of patients at more than one year.[64] The VC and MBC did not change appreciably in asymptomatic patients.[63] The chest roentgenogram may show a generalized or localized ground glass appearance, patchy infiltrates, dye in the thoracic duct, dye in the pulmonary arteries, or signs of pulmonary infarction.[64]

The signs and symptoms of the oil embolus resolve rapidly, but the oil may be demonstrable in the sputum as long as 6 weeks after the study,[65] and the decrease in the diffusing capacity may persist longer.[64]

Illicit drugs

Other than the pharmacologic effects, adverse pulmonary effects of illicit drugs depend primarily on the contaminants found in the drugs and the route of administration. Heroin will be used as a model for problems that occur due to intravenous administration (*Table 4*), with the understanding that identical reactions will be seen in patients misusing such drugs as tripelennamine or paregoric, since the reactions are mainly due to injected contaminants and marijuana when inhaled.

Of the major medical complications of heroin use, 21% were related to the pulmonary system in one study[66] (*Table 4*). Areas of atelectasis[67] and depressed diffusing capacities[68] can be seen on the roentgenograms in asymptomatic addicts. The cause of the atelectasis is believed to be periods of hypoventilation and infrequent sighs.

Table 4. Pulmonary complications of heroin use

Asymptomatic chest roentgenography abnormalities
Asymptomatic pulmonary function testing abnormalities
Respiratory depression
Noncardiogenic pulmonary edema
Pneumonia
Pulmonary embolus/infarction
Foreign body reactions with vasculitis, granulomas, and fibrosis
Increased risk of tuberculosis
Mycotic aneurysms of pulmonary arteries

Noncardiogenic pulmonary edema is the most commonly observed pulmonary problem (at least acutely) in some series. It was claimed to be the mechanism responsible for 87% of all narcotic deaths in 1964 in the United States.[69] Attempts to define the cause are still speculative; it occurs with overdoses administered by the intravenous and intranasal routes and with the oral use of drugs such as methadone[69] and propoxyphene.[70]

Symptoms may begin within minutes or be delayed for several hours.[71] Superimposed bacterial infections are said to occur in 50% to 75% of patients.[21] The chest roentgenogram typically demonstrates bilateral alveolar infiltrates, but it may be clear[71] or the infiltrates may be unilateral,[72] lobar,[72] primarily interstitial,[73] or have a batwing distribution.[73] The pattern of pulmonary edema may also shift from one segmental area to another.[73] Treatment is with narcotic antagonists, but is mainly supportive and anticipatory. The chest roentgenogram usually clears by the fifth day unless there is a superimposed pneumonia. The PFTs show a restrictive defect and a depressed D_LCO in 50% of

the patients with slow reversal over a 10- to 12-week period.[74]

Pneumonia may be related to the respiratory depression, central nervous system depression, noncardiogenic pulmonary edema, aspiration, or to resuscitative attempts by friends.[66, 72] Pulmonary emboli may arise from areas of septic thrombophlebitis or right-sided endocarditis; they may be bacterial or mycotic; and they may be a reflection of injection of foreign material, which lodges in the pulmonary microcirculation. They may present as typical emboli, septic emboli with cavitation, infarction or as a result of an inflammatory reaction.[66, 68, 72, 73]

Heroin is cut or diluted with talc, quinine, lactose, mannitol, baking soda, or other agents, and is filtered through cotton. Talc is also used as a filler in some tablets intended for oral use, e.g., meperidine or tripelennamine, and may produce the same reaction when crushed, mixed, and injected intravenously. A lung biopsy specimen can show foreign body granulomas associated with arteriolar thrombosis and interstitial fibrosis, which may lead to angiothrombotic pulmonary hypertension.[66, 72] An immunologic mechanism may be responsible for the arterial or interstitial disease. Recently, six patients dying of heroin-induced pulmonary edema were found to have immune deposits. Of these six patients, multifocal granular alveolar-septal deposits of IgM were seen in six; C3 in five; IgG in four; fibrinogen in three; and IgA in two.[75] The major symptom is dyspnea on exertion, which develops insidiously.[68] The chest roentgenogram shows progressive interstitial fibrosis.

A mycotic aneurysm of the pulmonary artery presenting as hemoptysis has been described as a complication of heroin addiction.[72] Increased incidences of infections such as tuberculosis[72] and tetanus[68] have also been described.

The most consistent complaint associated with inhalation of marijuana smoke is sore throat; others are bronchitis, sinusitis, rhinopharyngitis, and asthma. The risk is related to the frequency of smoking and the individual susceptibility of the patient. Other symptoms include dyspnea on exertion and exercise intolerance. Physical examination may reveal wheezes and crackles.[76]

The risk of conditions developing known to be associated with the inhalation of cigarette smoke such as emphysema, chronic bronchitis, and bronchogenic cancer is unknown. A study was performed on six high-dose hashish smokers (four were cigarette smokers); the vital capacity was reduced from 15% to 40%, and histologic findings of the pulmonary tissue showed abnormal respiratory mucosa with atypical cells, loss of cilia, and epithelial cell hyperplasia.[76]

Marijuana may be contaminated by fungi, which may produce either infection (chronic granulomatous disease developed in one patient who had an aspergillus infection)[77] or pulmonary colonization (allergic bronchopulmonary aspergillosis developed in an asthmatic patient).[78]

Mexican marijuana is presently being sprayed with paraquat, a herbicide known to cause, acutely, the adult respiratory distress syndrome and, chronically, pulmonary interstitial fibrosis with oral ingestion. The health implications of burnt, inhaled paraquat are unknown,[79, 80] but a recent study showed that the intrabronchial deposition of paraquat was directly toxic to the bronchial mucosa.[81] Marijuana is, at times, laced with other drugs, e.g., phencyclidine (PCP), a sedative used mainly in large animals. Again, it is not known

whether smoking these drugs causes any deleterious pulmonary side effects.

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