Drug-induced infiltrative lung disease

Ph. Camus, P. Foucher, Ph. Bonniaud, K. Ask


ABSTRACT: An increasing number of drugs are recognized to induce distinctive patterns of infiltrative lung disease (ILD), ranging from benign infiltrates to life-threatening adult respiratory distress syndromes. In addition to drugs, biomolecules such as proteins and cytokines, and medicinal plants are also capable of inducing respiratory disease, some being severe and/or irreversible.

For several reasons it is difficult to estimate the exact frequency of drug-induced infiltrative lung disease (DI-ILD). The risk for DI-ILD and the clinical patterns vary depending on a variety of host and drug factors.

Although establishing the diagnosis is often difficult, systematic evaluation of the possible role of almost any kind of drugs in ILD is warranted, as stopping a drug may favourably influence prognosis. However, prognosis depends on the drug and the type of DI-ILD. Corticosteroids may suppress the inflammatory reaction, but for many drugs, proof of the effect of corticosteroids is lacking.

Advances in prevention and prediction are needed. A user-friendly database of respiratory adverse drug reactions was made available on the web, to provide quick information in this area.

Eur Respir J 2001; 18: Suppl. 32, 93s–100s.

In the relatively recent past, conventional (i.e. nonillicit) drugs (as opposed to medical or surgical procedures) have emerged as relatively common and significant inducers of diffuse infiltrative lung disease (ILD) [1–5], as well as of pleural and pulmonary vascular disease [5–7]. Here, the term "infiltrative" will be preferred to "interstitial", as drugs can induce alveolar filling processes, in addition to affecting the interstitium [8–10]. Drugs as aetiological agents of ILD are interesting for two main reasons: 1) they offer a coherent explanation to a sizeable number of ILD cases seen in clinical practice [11]; and 2) early withdrawal of the causative drug will often lead to improvement or even cure of the ILD.

In addition to the utility of a catalogue of causative drugs and clinical pictures, at present [5, 11], it is necessary to look ahead, and to ask further questions in order to prepare the future of iatrogenic lung disorders. It is beyond the scope of the present paper to review all drug-induced respiratory diseases [11–13], but rather to point out novel aspects, and raise questions that need to be addressed. For a more complete overview of drug-induced respiratory diseases, refer to the Pneumotox® website [11] and to comprehensive review articles [1–3, 14].

Data Processing

From 1950 onwards, a considerable amount of information on drug-induced (DI)-ILD has been gathered [15], and made available to the clinician, as regards which drugs can cause adverse effects in the lung, and what pattern of lung reaction can be expected with the use of a given drug [1–4, 14, 16–18]. During that period of time, accrual of information has been almost relentless [15]. In addition, novel patterns of respiratory involvement and newer offending compounds have been described, as new drugs or combinations were made available to the clinician, and postmarketing experience on drugs expanded.

In the past, information on DI-ILD was essentially available in the form of conventional articles [1–5]. A supplemental source of information was recently provided, in the form of the free and continuously updated Pneumotox® website [11]. The site was designed and constructed to provide the interrogator with quick and easy access to formatted data, and relevant literature on drug-induced respiratory disease. At the time of writing, the site’s database contained 4,320 references on DI-ILD available on-line. An overview of this accumulated literature shows marked heterogeneity in reports. This illustrates the need to improve existing diagnostic criteria [19] and to provides publication guidelines for all reports on DI-ILD in the future.

In addition to drugs, biomolecules can also induce ILD, and include the following. 1) Interferons (used in the treatment of chronic myelogenous leukemia and of hepatitis C), which have been linked to the...
development of cutaneous or thoracic sarcoidosis [20–23] or bronchiolitis obliterans with organizing pneumonia (BOOP) [24]; this is of interest to the general understanding of the pathogenesis of these diseases. 2) Immunoglobulins and anti-thymocyte globulin, which may induce pulmonary infiltrates or pulmonary oedema [25, 26]. 3) Substances which modulate the growth, release or maturation of blood cells or progenitors, which have been shown to induce severe ILD, and even the acute respiratory distress syndrome (ARDS); examples include all-trans-retinoic acid (ATRA) [27, 28], used in the management of promyelocytic leukemia, and granulocyte (G)- or granulocyte-monocyte (GM)-colony stimulating factor (CSF) [29, 30], used to restore white blood cell counts in patients with bone marrow hypoplasia, mainly of iatrogenic origin. 4) Transfusions, which can induce the transfusion-related lung injury (TRALI) syndrome, which consists of the rapid development of pulmonary infiltrates or pulmonary oedema, following transfusion of blood or blood products containing antileukocyte or antihuman leukocyte antigen (anti-HLA) antibodies of donor origin [31, 32]. 5) A novel pattern of pulmonary complications has been described following stem cell transplantation, in the form of pulmonary cytolytic thrombi originating from donor cells [33].

Thus, whereas DI-ILDs were formerly regarded as interstitial tissue reactions to drugs, the three latter patterns suggest that they may also result from damage to pulmonary vessels, during the transit, aggregation and/or sequestration of activated blood cells or progenitors within the pulmonary circulation.

Treatments with natural products, such as herbs and other “dietary supplements”, will also require close attention, as they increasingly appear capable of causing serious diseases [34–37]. Well-documented examples are the association of the intake of ephedra with acute hepatitis, of aristolochic acid in a chinese herb containing Saurops androgythus with bronchiolitis obliterans [38–42].

Demographics and epidemiology

It is difficult to estimate the exact frequency of DI-ILD for several reasons, including the following. 1) The use of plain chest radiography is likely to underestimate subclinical forms of DI-ILD, compared with high-resolution computed tomography (HRCT) [43]. This has been exemplified by asymptomatic patients taking amiodarone [44], who may have opacities detectable at HRCT or at autopsy [45]. 2) Many drugs that induce ILD are used primarily by nonrespiratory physicians [46–49], and underdiagnosis is possible. 3) In oncology patients, where DI-ILD is common and the differential diagnosis is broad, the ultimate diagnosis will often remain presumptive, because the severe clinical status of the patient precludes the use of invasive diagnostic techniques. The role of drugs in the pathogenesis of the “delayed pulmonary toxicity syndrome” seen in this context remains to be delineated [50–53]. 4) Estimates of DI-ILD frequency would require systematic notification of drug-induced adverse effects to centralized drug-monitoring agencies (as performed in several countries, including France; but a Europe-wide reporting system is needed), and estimates of the number of exposed patients. Therefore, any estimate of the frequency of DI-ILD is probably an underestimate.

Risk factors

A major, but largely unresolved question is why, out of the treated population of patients, only some individuals will develop DI-ILD (see the report by NEMERY et al. [54] in this Supplement). A limiting dose has only been identified for a few drugs [55]. For amiodarone and bleomycin, toxicity was once considered likely only if high doses had been administered, but several recent reports of side-effects after low doses of these drugs tend to suggest that there is no real safe dose [56, 57]. For most drugs there is no apparent role of dosage or duration of treatment in relation to the likelihood of developing adverse effects, i.e. development remains largely unexpected and idiosyncratic.

Other explanations for the unequal risks among patients include the following. 1) Prior respiratory reactions to the drug, to a congener, or to unrelated compounds. Beyond occasional mentions in case reports [58–62], little data are available in that area. 2) Type of underlying disease for which the drug is being given. Diseases such as rheumatoid arthritis [63] or ulcerative colitis [50], may increase the relative risk of developing respiratory disease from disease-modifying drugs. 3) Occupational factors, such as exposure to asbestos, which may potentiate the noxious respiratory effects of ergot drugs [64–66]. 4) Activation and detoxication pathways of drugs and chemicals, which differ quantitatively and qualitatively among individuals [67]; also, some ethnic groups may be at increased risk of developing adverse reactions to drugs [46, 68–70]. 5) Hepatic or systemic reactions to drugs were occasionally linked to acetylator or HLA phenotype [71], but in contrast to these, very few studies have addressed the possibility of such a relation in patients with DI-ILD. The overall rarity and scattering of cases may be an explanation of why such analysis has not yet been possible. 6) The role of drugs taken concomitantly may be important, via their possible impact on cytochrome P450 systems, or via altered pharmacokinetics of the offending drug [72]. More information is needed in this area. 7) Hazardous associations have been reported, such as the concurrent administration of several chemotherapeutic agents, of chemotherapy and radiation, and of chemotherapy (even remote) with high inspired concentrations of oxygen. Inadvertent mixing of potentially pneumotoxic treatments may lead to an unexpected pulmonary toxicity, known as recall pneumonitis [73–76], which may develop at doses of each offending agent individually considered to be safe and nontoxic. 8) Bleomycin may exhibit
enhanced pulmonary toxicity in a patient with renal failure [77]. On the other hand, a slow, as opposed to a rapid infusion, may decrease the likelihood of bleomycin pulmonary toxicity [78].

Although these risks are well recognized, it is unclear that all these hazards are really taken into account and implemented sufficiently in clinical practice.

There are also examples of individuals who suffer in their risk of developing pulmonary disease following an apparently similar pulmonary insult [79]. For instance, why only a fraction of patients with definite amiodarone pneumonitis will ultimately develop irreversible pulmonary fibrosis, while others will recover, remains largely unexplained.

Despite identification of some risk factors, prediction of a DI-ILD remains difficult. Only for a limited number of drugs (bleomycin, nitrosoureas, amiodarone), is monitoring of patients who receive the drug advisable, but even this is debatable [80].

Clinical patterns

The clinicoradiographical correlates of DI-ILD range from subclinical opacities [81] to a picture of white lungs with the criteria of ARDS [11, 82, 83]. Several drugs (including amiodarone, bleomycin, colony stimulating factors, methotrexate, mitomycin, nitrofurantoin) [11], and several histopathological patterns (acute cellular-type nonspecific interstitial pneumonia, acute eosinophilic pneumonia, acute organizing pneumonia (alternatively called BOOP), acute pulmonary oedema or alveolar haemorrhage) may lead to the clinicoradiographical and gas-exchange pattern of ARDS [11]. Accordingly, pulmonary physicians should inform their colleagues in the intensive care field, that drugs can cause life-threatening respiratory failure and ARDS.

In the patient with migratory opacities with or without chest pain that could be suggestive of organizing pneumonia, a careful drug history should also be taken, as this clinical pattern may relate to exposure to drugs, or radiation [84–86].

Among the mild forms of DI-ILD, transient infiltrates have been described following administration of drugs (such as hydrochlorthiazide, nitrofurantoin, novel anticancer agents) [87], proteins [26], colony stimulating factors [29], and blood products [31]. Understandably, the histopathological background of these transient and benign infiltrates remains almost unknown [88], as no biopsy was taken in these cases.

While in most instances, the pulmonary reaction in DI-ILD is confined to the lung, or restricted to the lung and liver [89], it may occasionally be part of a generalized and systemic syndrome [60, 90–95]. Examples, include the following. 1) The drug-induced systemic lupus erythematosus syndrome [96], which may result from exposure to a wide array of drugs [11] (e.g. hydralazine, beta blockers, nonsteroidal anti-inflammatory drugs and many others). 2) Drug-induced hypersensitivity syndromes, with involvement of liver, brain, heart, digestive system, bone marrow, lymph nodes or any combination of these, which mostly follows the exposure to anticonvulsants [60, 94, 95, 97, 98]. 3) Drug-induced alveolar haemorrhage with concomitant renal failure from penicillamine [99]. 4) ANCA-positive drug-induced angitis with or without pulmonary capillaritis and haemorrhage, recently related to the use of the antithyroid drug propyl-thiouracil [100–105], in addition to a few other compounds [106–109]. 5) The drug-induced Churg–Strauss syndrome, occasionally described in the past following the use of aspirin [110], macrolides [111, 112], and more recently described in asthma patients on leukotriene antagonists [111–114].

Children may also develop DI-ILD [115]. Chemotherapy, radiotherapy or their combination in early childhood, for instance for brain tumours or lymphoma, may lead to a pattern of progressive pulmonary retraction and fibrosis [116]. The pulmonary maldevelopment may be aggravated with growth, and lead to impaired lung function and loss of functional reserve, resulting in lung transplantation in adolescence, or in early adulthood.

Histopathology

Reports of DI-ILD in which histological data were obtained (<10% of those published to date [11]) indicate that drugs can induce many distinctive histopathological patterns of ILD (table 1). In the constellation of ILD patterns described [140–142], most can be induced by drugs. Only giant-cell interstitial pneumonia and respiratory bronchiolitis–interstitial lung disease have not (yet) been related to exposure to drugs. While drugs can trigger the development of such conventional patterns of ILD as nonspecific interstitial pneumonia (cellular or fibrotic), eosinophilic pneumonia [59], or pulmonary fibrosis [143], drugs can also elicit less usual patterns such as organizing pneumonia (OP, previously designated BOOP) [86, 122, 144], or desquamative interstitial pneumonia (DIP) [124]. The two latter patterns have such a limited number of other recognized causes that the iatrogenic cause for the ILD is sometimes suspected as a result of the histological report. Other than mineral oil pneumonia [145] and, sometimes, amiodarone pneumonitis [146], the histopathological appearance of DI-ILD is almost indistinguishable from that of their counterparts occurring idiopathically, or from other causes.

While some drugs (e.g. minocycline, nitrofurantoin) induce quite stereotyped reactions in the lung (eosinophilic pneumonia and the cellular type of nonspecific interstitial pneumonia, respectively) [11], other drugs (e.g. amiodarone, bleomycin), can induce a palette of variegated histopathological patterns in different patients [11]. As an example, patterns described under the term "amiodarone pneumonitis" may include nonspecific interstitial pneumonia (cellular or fibrotic type), alveolar filling by foamy macrophages, organizing pneumonia, diffuse alveolar damage, interstitial lung fibrosis, a pattern of "usual interstitial pneumonia", or some combination thereof depending on the patient and, possibly, the site of the lung biopsy [11, 146]. The reasons why some drugs
are capable of inducing several patterns of ILD, and why a given patient will develop a given pattern remain unknown.

A notable clue that suggests the drug as a cause, is the fact that the ILD (e.g. nonspecific interstitial pneumonia, organizing pneumonia) will demonstrate a relative refractoriness to steroids, or will recur while the patient is still receiving relatively high dosages of steroids [124]. Of note, long-term treatment with steroids, which are occasionally needed to control severe DI-ILD, expose the patient to significant risks, including that of severe opportunistic infections in the lung or elsewhere.

### Future outlook

In order to improve current knowledge of DI-ILD, and to have it move beyond the purely descriptive art, which was necessary up to now, it is necessary to: 1) refine and homogenize the diagnostic criteria of all forms of drug-induced respiratory diseases among different countries, to give future publications a common and interpretable framework; 2) help develop and serve drug monitoring systems, in conjunction with responsible agencies, be they country-based or European, with the objective of exhaustively collecting and formatting data on drug-induced adverse respiratory reactions; 3) collect data on associated or other risk factors, including genetic profile, occupational exposure, history (even remote) of exposure to drugs [151]; and 4) evaluate the long-term consequences of drug-induced respiratory diseases, in order to better guide pulmonary physicians in the management (including the handling of steroids) and follow-up of afflicted patients.

With these data at hand in the future, broader understanding, better prevention, earlier detection, and overall reduction of the severity of drug-induced infiltrative lung disease should follow. This may help lawmakers to accurately delineate fields of responsibility, and prepare ways to compensate patients adequately.

### Imaging

The pattern and topographic distribution of opacities in patients with DI-ILD are highly variable. Occasionally, imaging features are very suggestive, if not pathognomonic, of certain types of DI-ILD. Examples include the "foamy" opacities of lipidic density seen on HRCT of patients with mineral oil pneumonia [9], and the asymmetrical, nonsegmental opacities common to many patients with amiodarone lung [147]. Other imaging features are suggestive of a given histopathological pattern of DI-ILD, like the migratory, occasionally painful opacities of BOOP [85], the "melted candlewax-like" opacities in nitrofurantoin lung or in some OP cases [43, 148], the image of "photographic negative of pulmonary oedema" of eosinophilic pneumonia [149], and the distinctive mosaic pattern of desquamative interstitial pneumonia [150].

### Table 1. – Types of infiltrative lung disease which may be induced by drugs (pulmonary oedema was omitted)

<table>
<thead>
<tr>
<th>Type of infiltrative lung disease</th>
<th>Prototypic drug(s)</th>
<th>Frequency</th>
<th>Severity</th>
<th>Literature</th>
<th>Number of causative drugs [11]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSIP-cellular</td>
<td>Methotrexate, nilutamide</td>
<td>Common</td>
<td>Mild</td>
<td>[18, 46]</td>
<td>89</td>
</tr>
<tr>
<td>Granulomatous IP</td>
<td>BCG, methotrexate</td>
<td>Uncommon</td>
<td>Mild</td>
<td>[18, 117, 118]</td>
<td>8</td>
</tr>
<tr>
<td>Pseudo-sarcoidiosis</td>
<td>Interferons (antiretroviral therapy?)</td>
<td>Uncommon</td>
<td>Mild</td>
<td>[20, 23, 119]</td>
<td>3</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>Antibiotics, NSAID, ACE inhibitors</td>
<td>Common</td>
<td>Can be severe</td>
<td>[58, 120, 121]</td>
<td>95</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>Amiodarone, bleomycin, interferons, nitrofurantoin, radiations, statins</td>
<td>Common</td>
<td>Can be severe</td>
<td>[83, 84, 122, 123]</td>
<td>23</td>
</tr>
<tr>
<td>DIP</td>
<td>Nitrofurantoin</td>
<td>Rare</td>
<td>Moderate</td>
<td>[124]</td>
<td>3</td>
</tr>
<tr>
<td>LIP</td>
<td>Phenytoin</td>
<td>Very rare?</td>
<td>Mild</td>
<td>[125]</td>
<td>1</td>
</tr>
<tr>
<td>NSIP-fibrotic, or IPF-like</td>
<td>Amiodarone, chemotherapy, ergots</td>
<td>Quite common</td>
<td>Severe</td>
<td>[8, 48, 126]</td>
<td>34</td>
</tr>
<tr>
<td>AIP/DAD</td>
<td>Chemotherapy, gold, methotrexate*</td>
<td>Quite common</td>
<td>Usually severe</td>
<td>[127–132]</td>
<td>10 and most chemotherapies</td>
</tr>
<tr>
<td>Alveolar filling process with foamy macrophage</td>
<td>Amiodarone, mineral oil</td>
<td>Quite common</td>
<td>Variable</td>
<td>[9, 10, 45]</td>
<td>2</td>
</tr>
<tr>
<td>Alveolar haemorrhage pulmonary haemosiderosis***</td>
<td>Anticoagulants, fibrinolytic agents, penicillamine, PTU</td>
<td>Unusual</td>
<td>Variable</td>
<td>[133–137]</td>
<td>25</td>
</tr>
<tr>
<td>Proteinosis-like</td>
<td>Busulfan</td>
<td>Rare?</td>
<td>?</td>
<td>[138, 139]</td>
<td>1</td>
</tr>
</tbody>
</table>

NSIP: nonspecific interstitial pneumonia; IP: interstitial pneumonia; DIP: desquamative interstitial pneumonia; LIP: lymphocytic interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; AIP: acute (or accelerated) interstitial pneumonia; DAD: diffuse alveolar damage; PTU: propyl-thiouracil; BCG: bacille Calmette-Guerin; NSAID: nonsteroid anti-inflammatory; ACE: angiotensin converting enzyme. *: as per gold or methotrexate, it may be difficult to distinguish "hyperdense" cellular NSIP, from true DAD; **: in addition, alveolar haemorrhage may complicate most cases of acute cellular interstitial pneumonia; ?: too few data available.

### Acknowledgements

The authors wish to thank C. Sartini-Camus for invaluable help in refining the manuscript.


