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CURRENT UPDATE

Drugs that may injure the respiratory system

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The above authors have founded a clinical study group known as the GEPPI (Groupe d'Etudes de la Pathologie Pulmonaire Iatrogene. Address: Professor Ph. Camus, Service de Pneumologie, CHU, BP 1542, F-21034 Dijon, France; fax: 33 3 80 29 32 51; e-mail: pneumo.dijon@planetb.fr). The purpose of this group is to provide information regarding individual cases, collect and update literature on drug-induced lung disease, publish updated lists of offending compounds, and formulate warnings when new side-effects of drugs are recognized. Thus, the present table may be subjected to update in the future in this Journal.

The number of drugs which have been shown to damage the respiratory system in some instances continues to increase. The clinical pattern of involvement from drugs is diverse and difficult to memorize accurately. Table 1 is designed to provide the information currently available on such drugs in a readily accessible form.

A good way of obtaining broad information on drug-induced respiratory disease is to refer to general articles and reviews on the topic. Many such papers have been available in the literature in the recent years [1–37].

Another method is to scrutinize the literature regarding any given drug. We considered that the preparation of a table listing most drugs capable of injuring the respiratory system was appropriate. The present table includes: 1) generic drug name (no trade name is provided); 2) clinical pattern of involvement, according to the types described in the legend; 3) a rough estimate of frequency of the adverse effect from each compound (*: isolated case reports which await confirmation; **: about 10 cases available; ***: 20–100 cases available; ****: >100 cases reported); 4) relevant references. Obviously, not all references for a given compound have been mentioned, because the overall list would have been too long. For example, references regarding pulmonary adverse effects from bleomycin total 114, and 135 for nitrofurantoin. No attempt has been made to validate the case histories quoted here.

Often, most if not all drugs from the same pharmacological category are likely to induce the same adverse effect in the lung. As an example, angiotensin-converting enzyme (ACE) inhibitors may induce cough [38], β-blockers may induce bronchospasm [35], nonsteroidal anti-inflammatory drugs may induce bronchospasm or eosinophilic pneumonia [39], and ergoline drugs may induce chronic pleural thickening or effusion [40].

A few compounds have been listed despite the fact that they were recalled or withdrawn from the market earlier (*e.g.* aminorex, hexamethonium, mecamylamine, practolol or tryptophan). There are several reasons for this: 1) disease from drugs such as I-tryptophan leave long-term sequelae and patients may still be seen with persistent illness from the drug; 2) the clinical picture (*e.g.* bronchiolitis obliterans organizing pneumonia (BOOP)) from classic drugs, such as hexamethonium or meca-mylamine, may be seen with newer drugs, such as penicillamine, gold or amiodarone; and 3) clinical pictures long thought to have vanished (*e.g.* pulmonary hypertension from the appetite suppresant, aminorex) have regained interest because similar newer compounds (*e.g.* fenfluramine) may induce the same adverse effect [41].

Contraceptive pills may induce varied changes in the pulmonary circulation [42–44], but the aetiological link is too weak to make it possible to blame one particular formulation or brand.

The field of drug-induced pulmonary infections and cancer, as well as the complications of illicit drug use and abuse have been deliberately omitted.

This list of drugs is available on a continuously updated Web page at: http://www.pneumotox.com/lungdrug.

For further comments, see the editorial in this issue of the Journal.

The summary of available information on drugs that may injure the respiratory system appears on the following pages.

Services de Pneumologie *Dijon, Montpellier, ‡‡St Etienne, #Marseilles, France. Services de Pharmacovigilance **Paris, +Montpellier, ++Dijon, ‡Chur (Switzerland), St Etienne$. ##Service de Gériatrie, Dijon, France

Table 1. – Summary of information available concerning drugs that may injure the respiratory system

Drug	Clinical pattern	Frequency	[Ref.]
acebutolol	I b, d; V a, b, c, d	**	[45]
ACE inhibitors	I c; IV a, d; VIII a	****	[46–50]
acetaminophen	I c; IV a	*	[51–53]
acetylcysteine	IV a	*	[54]
acetylsalicylic acid (aspirin)	I c; II a, b; III a; IV a, b; VII b; X	***	[55]
acrylate	VI a	**	[56]
acyclovir	I b; Va, b, c	*	[57]
adenosine	IV a	*	[58]
adrenaline (epinephrine)	II a	*	[59]
albuterol (see salbutamol)	II a	*	[60–62]
allopurinol	VI d	*	[63]
aminoglycoside antibiotics	IX a	**	[64]
aminorex (recalled in early 1970)	VI b	****	[65]
amiodarone	I b, c, d, g, k; IV a; V a, c, d	****	[21, 22, 66–74]
amitryptyline	II a, b	*	[75]
amphotericin B	I d; II a, b	*	[76–79]
ampicillin	I b, c	*	[80]
amrinone	I b	*	[81]
antilymphocyte globulin	II a	*	[82]
L-asparaginase	IV a, b; VI a	*	[83–85]
aurothiopropanosulphonate (gold salt)	I a, b, c, d; IV c	***	[86–93]
azapropazone	I b	*	[39, 94]
azathioprine	I b	**	[95]
BCG therapy	I b	**	[96]
bepridil	I g	*	[97]
betahistine	IV a	*	[98]
bleomycin	I b, c, d, g, k; II b; V f; VI c; VII a; XI b	****	[99–107]
blood transfusions	II a	***	[108–114]
bromocriptine	V a, c	***	[40]
bucillamine	I c; IV d	*	[115]
busulphan	I e, g; VI c	***	[20]
cabergoline	V a, c	*	[40]
calcium salts	I i	**	[116, 117]
captopril	I b, c, f; IV d; VIII a	****	[50]
carbamazepine	I b, c, k; II a; III a; V d; VII a, b; X	***	[46, 118–125]
carmustine	I g; II b; V a, f; VI c	***	[32, 126]
celiprolol	I a	*	[45]
cephalosporins	I c, d; IV a, b	*	[127–129]
chlorambucil	I b	**	[130]
chlorpromazine	I c; II a; V d; VI a	*	[131, 132]
chlorpropamide	I c	*	[133]
ciprofloxacin	IV b	*	[134]
clofazimine	I h	*	[135]
clofibrate	I c; V d	*	[136]
clomiphene	II a, b; V a; VI a	**	[137, 138]
clonidine	Vd	*	[139]
colchicine	II a; X	*	[140]
contraceptives (oral)	VI b, c	***	[43, 44]
contrast media	I c; II a, b; IV a, b	****	[141–145]
co-trimoxazole	I b, c; II a	**	[146, 147]
cromoglycate	I b, c	*	[148]
curare	IV a, b	***	[129, 149]
cyclophosphamide	I c, g; II a; IV a, b. V a	***	[150–154]
cyclosporin	I j; II a; III a; VI b	*	[155–159]
cytarabine	II b; III a	**	[160–164]
dantrolene	V b	*	[165, 166]
dapsone	XI a	*	[167]
deferoxamine	I c; II a, b; VI a	**	[168–171]
desipramine	I c; IV a	**	[172–174]
dexamethasone	II a	**	[175]
dexfenfluramine	I b; VI b	***	[176–178]
diclofenac	I c, IV a	**	[39, 179, 180]

Continued over...

Drug	Clinical pattern	Frequency	[Ref.]
dihydralazine	I b, d; V a, d	**	[39, 181–185]
dihydro-5-azacytidine	XI c	**	[186]
dihydroergocristine	V a, c	*	[40]
dihydroergocryptine	I b, d	*	[40]
dihydroergotamine	I d	*	[40]
diltiazem	II a	*	[187]
l-DOPA	VII b; IX b	*	[188, 189]
dothiepin	I b, g	*	[190, 191]
enalapril	IV d; VIII a	**	[192, 193]
ergometrine	IV a	*	[194]
ergotamine	I b; V a	**	[40]
erythromycin	II a, b	*	[195]
ethambutol	I c	*	[196]
ethchlorvynol	II a; V a	*	[131, 197]
etoposide	XI b (due to coronary spasm)	***	[198, 200]
fenbufen	I c, VII a	*	[39, 200–202]
fenfluramine	I b; VI b	***	[176–178]
fenoprofen	I c	*	[39, 205]
flecainide	I b	*	[204]
floxuridine	I b	**	[205]
fludarabine	I a; II b	*	[206, 207]
fluoxetine	I b	**	[209–212]
flurbiprofen	IV a	*	[208]
furazolidone	I c	*	[213]
glafenine	1 c	*	[214]
glibenclamide	III a; X	*	[215]
G(M)-CSF	I b, c; II b	***	[216–211]
haloperidol	II b	*	[222]
heparin	II b	*	[223]
hexamethonium (discontinued)	I d	***	[224]
hyralazine	I b, d; III a; V a, d; VI b	**	[181–183, 225–227]
hydrochlorothiazide	I b; II a, b	***	[228–234]
hydrocortisone	IV b	*	[129]
hydroxyquinoline	I b	*	[235]
hydroxyurea	I b	**	[236]
ibuprofen	I c, II a	*	[39, 202, 237, 238]
ifosfamide	I b	*	[239]
imipramine	I c	**	[240]
immunoglobulins (IVIG)	II a; IV b	**	[129–241]
indomethacin	IV b	*	[129]
interferon alpha	I b, d, e	**	[242–245]
interleukin 2	II a, b; IV a, b; IV a, b	**	[246–248]
iodine, radiographic contrast media	I c, j; II a; V a; IV b	****	[141–145]
isoniazid	I c; V d	**	[249, 252]
isotretinoin	I c, IV a; V b	**	[253, 254]
itraconazole	V c		[255]
labetalol	I g	*	[256, 257]
leuprorelin	II b	*	[258]
lidocaine	II a; IV b	*	[129, 259]
lisinopril	VIII a	**	[260]
lisuride	V a, c	*	[261]
lomustine	I g, VIc	**	[32]
loxoprofen	I c; IV a	*	[39, 262, 263]
lupron	V e	*	[264]
maprotiline	I b	*	[265]
mecamylamine (discontinued)	I d	**	[266]
medroxyprogesterone	I g	*	[267]
melphalan	I c, g; IV a	**	[268–271]
mephenesin	I c	*	[272]
mercaptopurine	I b	*	[273]
mesalamine	I c, d; XI b	**	[274]
metapramine	I b	*	[275]
methadone	II a	*	[276, 277]
methotrexate	I a, b, c; II a; IV b; V a; XI b	****	[29, 278–281]

Continued over...

Drug	Clinical pattern	Frequency	[Ref.]
methyldopa	V d; VII b	**	[30, 282]
methysergide	I b; V a, c; VIId, XI b	**	[40, 283, 284]
metoclopramide	IV a	*	[285]
metoprolol	IV a; VI b	*	[286]
metronidazole	I c	*	[287]
miconazole	II b	*	[288]
minocycline	I c, d, k; VII b; X; XI b, c	***	[289–295]
mitomycin C	I b, g; II b, c; III a; VI b	***	[296–304]
mitoxantrone	I b	*	[305]
moxalactam	III a	*	[306]
nadolol	I b	*	[307]
naftidrofuryl	IV a	*	
nalbuphine	II a	**	[308, 309]
nalfon	Ic	*	[203]
nalidixic acid	I c	*	[310]
naloxone	II a	**	[311, 312]
naproxen	I c, IV a	*	[39, 180, 202, 313]
nicergoline	V a, c; XI b	**	[40]
nilutamide	I a, b, c, d	***	[35, 37]+
nitrofurantoin	I a, b, d, e; III a; IV a, b; V a, d; VI d; VIII b; X; XI b, c	****	[93, 314–321]
nitroglycerin	II a	*	[322]
nitrosoureas	I g, VI c	***	[32, 323]
nomifensine	I b, c	*	[324, 325]
NSAIDs	I c; IV a; X	***	[39]
noramidopyrine	II a	*	[326]
oxprenolol	I b, IV a; V a, c	*	[45, 327, 328]
oxyphenbutazone	I b	*	[39, 329]
paclitaxel	I b; IV a	**	[330, 331]
para(4)-aminosalicylic acid (PAS)	I c; II a	**	[274, 332]
paraffin (mineral oil)	I j	****	[333–337]
penicillamine	I b, c, d, g; III b; IV a, c; V c	***	[338, 339]
penicillins	I c; IV a, b; VI d; VII a, b	*	[129, 340–347]
pentamidine	I c; IV a	*	[348, 349]
perindopril	I c	*	[47]
phenylbutazone	I c; II a; VII a	*	[39, 350–352]
phenytoin	I b, c, f, k; II a, c, d; VI a, d; VII a, b	***	[353–360]
piroxicam	I c	*	[39]
pituitary snuff	I b	*	[361]
polyethylene glycol	II b; IV a	*	[362]
practolol (recalled)	I b; V b, c	***	[45, 363]
praziquantel	V a	*	[364]
procainamide	I b; V a; d; VI a	***	[365–368]
procarbazine	I a, b	*	[369–373]
propafenone	IV a	*	[374]
propoxyphene	II a	*	[375]
propranolol	I c; V a, d; VI b	**	[45, 286, 376, 377]
propylthiouracil	I c, k; II b; V a, b; VI d	**	[378–381]
prostglandin F2-α	IV a	*	[382]
protamine	IV b; VI b	**	[129, 383]
pyrimethamine-dapsone	I c; X	*	[384–387]
pyrimethamine-sulphadoxine	I b, c; II a	*	[385, 387]
quinidine	I b; III a	*	[388, 389]
radiations	I b, d, g; II b; V a, c, f; VI c; VII d	****	[390–397]
retinoic acid	I b; II a, b	**	[398–400]
ritodrine	II a	**	[60]
salbutamol	II a; IV a	***	[60–62]
simvastin	I b; d; V a	*	[401]
steroids	VII c; IX a	***	[402, 403]
streptokinase	IIb; III a; IV a	**	[404]
streptomycin	I c	**	[249, 405]
sulindac	I c; X	*	[39, 414–417]
sulphamides-sulphonamides	I b, c; II a, b; IV a, b; V d; VI d; VII b	***	[30, 406–413]

+ see also: Pfitzenmeyer P, Foucher P, Piard F, *et al*. Nilutamide pneumonitis: a report on eight patients. *Thorax* 1992; 47: 622–627.

Continued over...

Drug	Clinical pattern	Frequency	[Ref.]
sulphasalazine	I b, c, e; II a; V b, d; VI d	***	[274, 409–413]
tamoxifen	I c, g; II a; IV a; VI a	*	[303, 418]
terbutaline	II a	**	[60]
tetracycline	I c; V d	*	[291, 419, 420]
thiopental	IV b	**	[129]
tiopronin	I b; IV c	*	[421, 422]
TNF-alpha	II a; III a	**	[423, 424]
tolfenamic acid	I c	*	[39, 425]
transfusions (blood, leucocytes)	II a	***	[108, 109, 111–114, 426]
triazolam	II a	*	[427]
trimethoprim	I c; II a; VII a	**	[146, 147]
trimipramine	I c; V b, f	**	[428]
troleandomycin	I c	*	[346]
L-tryptophan (recalled)	I c; VI b, d	****	[429–432]
D-tubocurarine	IV a, b	***	[129]
urokinase	III a; IV a	*	[433]
vancomycin	IV b	*	[129]
vasopressin	II a	*	[434]
vinblastine	I c, k; II b; IV a, b	***	[299, 435–438]
vindesine	I b, IV a, b	**	[438, 439]
venorilbine	II a; IV a	*	[440]
vitamin D	I i	*	[441]
warfarin	II a; V e; VIIIb	***	[422–445]
zomepirac	IVa	*	[446]

ACE: angiotensin-converting enzyme; BCG: bacille Calmette-Guérin; L-DOPA: L-dihydroxyphenylalanine; G/M-CSF; granulocyte/macrophage colony-stimulating factor; IVIG: intravenous immunoglobulins; NSAIDS: nonsteroidal anti-inflammatory drugs; TNF-α: tumour necrosis factor-α.

I: interstitial lung disease (with diffuse (D) or focal (F) roentgenological changes). a) acute hypersensitivity pneumonitis and respiratory failure (may transiently behave like adult respiratory distress syndrome (ARDS)) (D); b) subacute interstitial lung disease (nonspecific; often lymphocytic bronchoalveolar lavage (BAL) pattern) (D); c) pulmonary infiltrates and eosinophilia (D, F)[$$]; d) organizing pneumonia ± bronchiolitis obliterans (BOOP) (D, F); e) desquamative interstitial pneumonia (DIP) (D)[$]; f) lymphocytic interstitial pneumonia (LIP) (D)[$]; g) pulmonary fibrosis (D)[$]; h) subclinical cytological changes in BAL cell composition; i) pulmonary calcification (D)[$]; j) mineral oil pneumonia (F-D)[$]; k) multiple lung nodules (usually, focal BOOP or, less often, vasculitis); $: opacities tend to predominate in basilar regions; $$: opacities tend to predominate in apices.

II: pulmonary oedema. a) acute pulmonary oedema; b) acute permeability oedema often accompanied by ARDS; c) acute permeability oedema, ARDS and the haemolytic and uraemic syndrome (almost specific to mitomycin C).

III: pulmonary haemorrhage. a) alveolar haemorrhage; b) Goodpasture-like syndrome.

IV: airways disease. a) bronchospasm; b) bronchospasm and anaphylactic shock; c) bronchiolitis obliterans; d) cough.

V: pleural changes. a) pleural effusion; b) eosinophilic pleural effusion; c) thickening ± pericardial thickening/effusion; d) pleural/pericardial thickening or effusion and positive antinuclear/antihistone antibodies, *i.e.* the drug-induced lupus syndrome; e) haemothorax; f) pneumothorax.

VI: vascular changes. a) thromboembolic disease (with or without antiphospholipid antibodies); b) pulmonary hypertension; c) pulmonary veno-occlusive disease; d) vasculitis.

VII: mediastinal changes. a) enlarged hilar/mediastinal lymph nodes; b) angioimmunoblastic lymphadenopathy-like syndrome/lymphoma; c) mediastinal fatty infiltration (mediastinal lipomatosis); d) sclerosing mediastinitis.

VIII: large airways involvement. a) acute upper airway obstruction and laryngeal oedema (see also bronchospasm and anaphylaxis under IVb); b) upper airway obstruction from peritracheal haemorrhage.

IX: muscle and nerves. a) lowered force generation; b) disordered breathing or respiratory movements (respiratory dyskinesia).

X: constitutional/systemic symptoms. Systemic hypersensitivity syndrome with a combination of skin rash, lymph node enlargement, eosinophilia, changes in liver chemistry and/or mental disturbances.

XI: varied effects. a) methaemoglobinaemia, cyanosis, elevated blood nitrates and respiratory failure; b) acute chest pain; c) acute chest pain and interstitial pneumonitis.

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