Table 22.2 Clinical features of COLD

	Predominant emphysema	*Predominant chronic bronchitis*
Age	60–69	50–59
Dyspnea	Severe	Mild
Cough	After dyspnea starts	Before dyspnea starts
Sputum	Scanty, mucoid	Copious, purulent
Bronchial infection	Less frequent	More frequent
Respiratory insufficiency episode	Often terminal	Repeated
Chest film	Increased diameter Flattened diaphragms	Increased bronchovascular markings, large heart
$Paco_2$ (mm Hg)	35–40	50–60
Pao_2 (mm Hg)	65–75	45–60
Hematocrit (%)	35–45	50–60
Pulmonary hypertension		
Rest	None to mild	Moderate to severe
Exercise	Moderate	Worsens
Cor pulmonale	Rare	Common
Diffusion capacity	Decreased	None to slightly decreased

Adapted from Ingram RH: Chronic bronchitis, emphysema, and airways obstruction. In Petersdorf RG, Adams RD, Braunwald E, et al (Eds): Harrison's Textbook of Internal Medicine. New York, McGraw-Hill, 1983, p 1548.

Table 22.1 Risk Factors for the Development of COLD

Major	*Minor*
Smoking	Air pollution
Age	Alcohol
Male sex	Race
Existing impaired lung function	Nutritional status
Occupation	Family history
α_1-Antitrypsin deficiency	Socioeconomic status
	Respiratory tract infections
	Bronchial reactivity

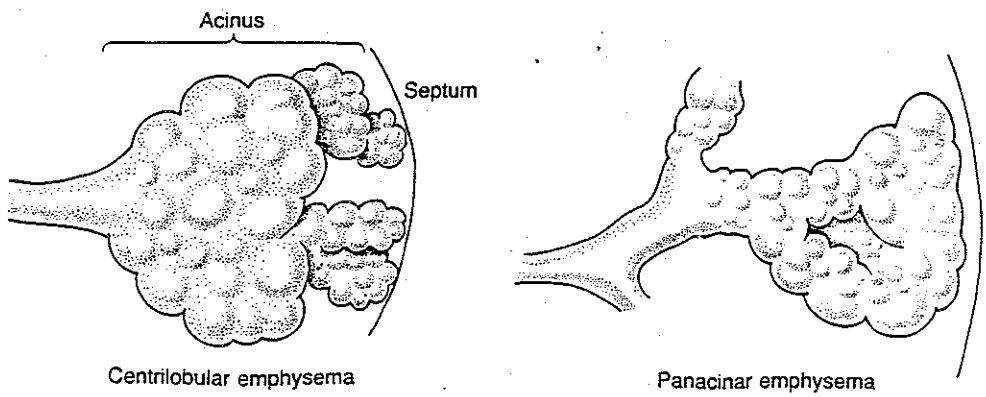
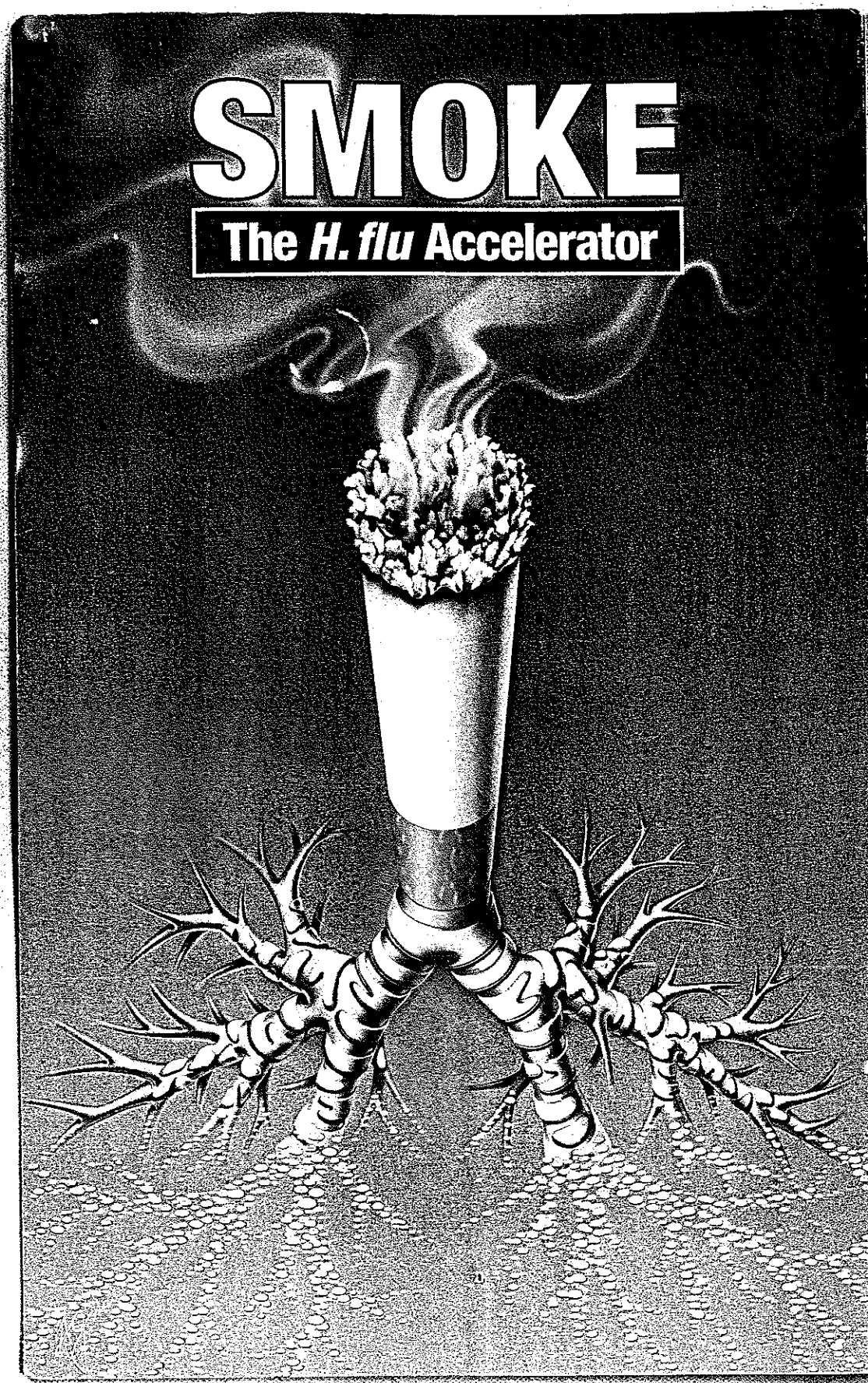


Figure 22.1 In centrilobular emphysema the terminal bronchioles are involved. In panacinar emphysema the entire acinus is involved.


SMOKE
The H. flu Accelerator

FEF = forced expiratory fraction
FEV = forced expiratory volume
TLC = total lung capacity
RV = residual volume
PEFR = peak expiratory flow rate

Boc 2

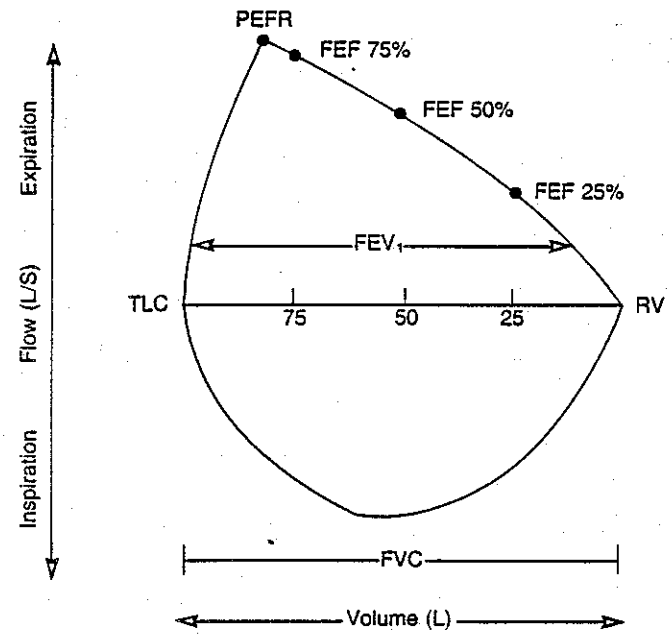


Figure 22.4 Flow volume loop (normal).

Figure 22.5 Flow volume loops of an obstructive and a restrictive pattern.

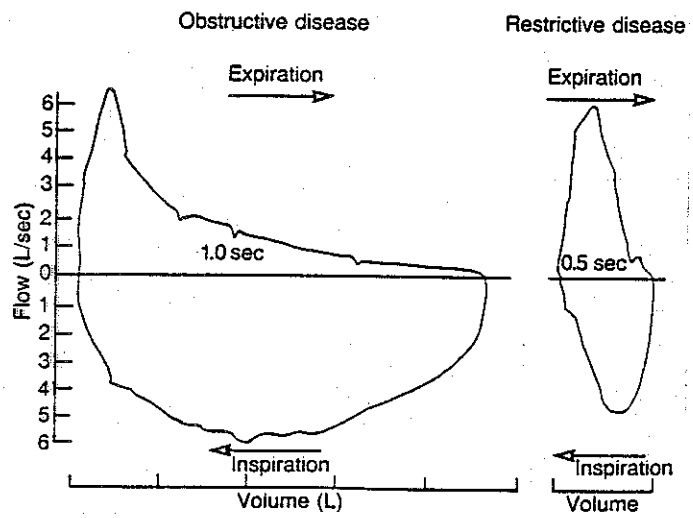


Table 22.3 Maintenance Doses of Aminophylline in Exacerbations of COLD

Age (>50 yr)	0.6–0.7 mg/kg/h
Bacterial or viral pneumonia	0.45–0.7 mg/kg/h
Left or right ventricular failure	0.45–0.7 mg/kg/h
Liver disease (total bilirubin > 1.5 mg/dL)	0.2–0.25 mg/kg/h

TABLE 98–2. Common Bacterial Pathogens Isolated From the Sputum of Patients With an Acute Exacerbation of Chronic Bronchitis

Pathogen	Estimated Incidence[a]
Haemophilus influenzae[b]	24–26
Haemophilus parainfluenzae	20
Streptococcus pneumoniae[c]	15
Moraxella catarrhalis[b]	15
Klebsiella pneumoniae	4
Serratia marcescens	2
Neisseria meningitidis[b]	2
Pseudomonas aeruginosa	2

[a]Expressed as percent of cultures.
[b]Often β-lactamase positive.
[c]Up to as many as 25% of strains may be intermediate or highly resistant to penicillin.

TABLE 98–1. Useful Classification System for Patients With Chronic Bronchitis and Initial Treatment Options[27]

Baseline Status	Criteria or Risk Factors	Usual Pathogens	Initial Treatment Options
Class I			
Acute tracheobronchitis	No underlying structural disease	Usually a virus	1st None unless symptoms persist 2nd Amoxicillin or a macrolide/azithromycin *
Class II			
Chronic bronchitis	FEV_1 > 50% predicted value, increased sputum volume and purulence	*Haemophilus influenzae, Hemophilus* sp. *Moraxella catarrhalis, Streptococcus pneumoniae* (β-lactam resistance possible)	1st Amoxicillin, or quinolone if prevalence of *H. influenzae* resistance to amoxicillin is > 20% 2nd Quinolone, amoxicillin–clavulanate, azithromycin, tetracycline, or trimethoprim–sulfamethoxazole
Class III			
Chronic bronchitis with complications	FEV_1 < 50% predicted value, increased sputum volume and purulence, advanced age, at least four flares/year, or significant comorbidity	Same as class II; also *Klebsiella pneumoniae Pseudomonas aeruginosa, K. pneumoniae,* and other gram-negative organisms (β-lactam resistance common)	1st Quinolone 2nd Expanded spectrum cephalosporin, amoxicillin–clavulanate, or azithromycin
Class IV			
Chronic bronchial infection	Same as for class III plus yearlong production of purulent sputum	Same as class III	1st Oral or parenteral quinolone, carbapenem or expanded spectrum cephalosporin followed by high-dose oral ciprofloxacin or routine dose trovafloxacin

1st = first choices; 2nd = alternate treatment options.
Quinolone: ciprofloxacin, clinafloxacin, grepafloxacin, trovafloxacin.
Tetracycline: tetracycline HCl, doxycycline.
Carbapenem: imipenem/cilistatin, meropenem.
Expanded spectrum cephalosporin: ceftazidime, cefepime.

Haemophilus

* sensibilité limite aux macrolides
(! les - erythromycine)
- télithromycine ...

* producteurs de β-lactamases

S. pneumoniae

- non producteurs de β-lactamases
MAIS
- sensibilité diminuée

⇒ dose ↑↑ d'amoxycilline

▶ PRINCIPLES OF PHARMACOTHERAPY

- COLD includes the terms *chronic bronchitis* and *emphysema*. Bronchitis is defined in clinical terms, whereas emphysema is defined in terms of anatomic pathology. Most patients have a combination of chronic bronchitis and emphysema.
- The most common cause of COLD is cigarette smoking. The first and most important step in the treatment of COLD is smoking cessation. Exercise rehabilitation also plays an important role in improving daily function in most patients.
- The main classes of drug treatment for COLD include anticholinergics, sympathomimetics, methylxanthines, and corticosteroids. Current clinical trends indicate use in that order.
- The foregoing therapies have demonstrated improvement in subjective and objective symptoms. However, it is unknown whether morbidity and mortality associated with COLD are decreased. The only treatment shown to increase survival is oxygen administered for most of the hours of the day.
- The treatment of COLD is not an exact science and is very patient dependent. For instance, some patients may respond better to one bronchodilator than another or may respond to pharmacologic agents via mechanisms other than bronchodilation.
- In COLD, combination treatments (e.g., anticholinergics and sympathomimetics) have been found to be more effective than either treatment alone.
- There continues to be great controversy regarding the most beneficial treatment of COLD, particularly regarding the use of corticosteroids and antibiotics for acute exacerbations.
- Many agents, particularly corticosteroids and methylxanthines, are not without considerable potential toxicity. Therefore, embarking on a pharmacologic plan for the treatment of COLD requires weighing the risk–benefit ratio carefully and having a comprehensive plan to assess subjectively and objectively the efficacy and toxicity of the chosen therapy.

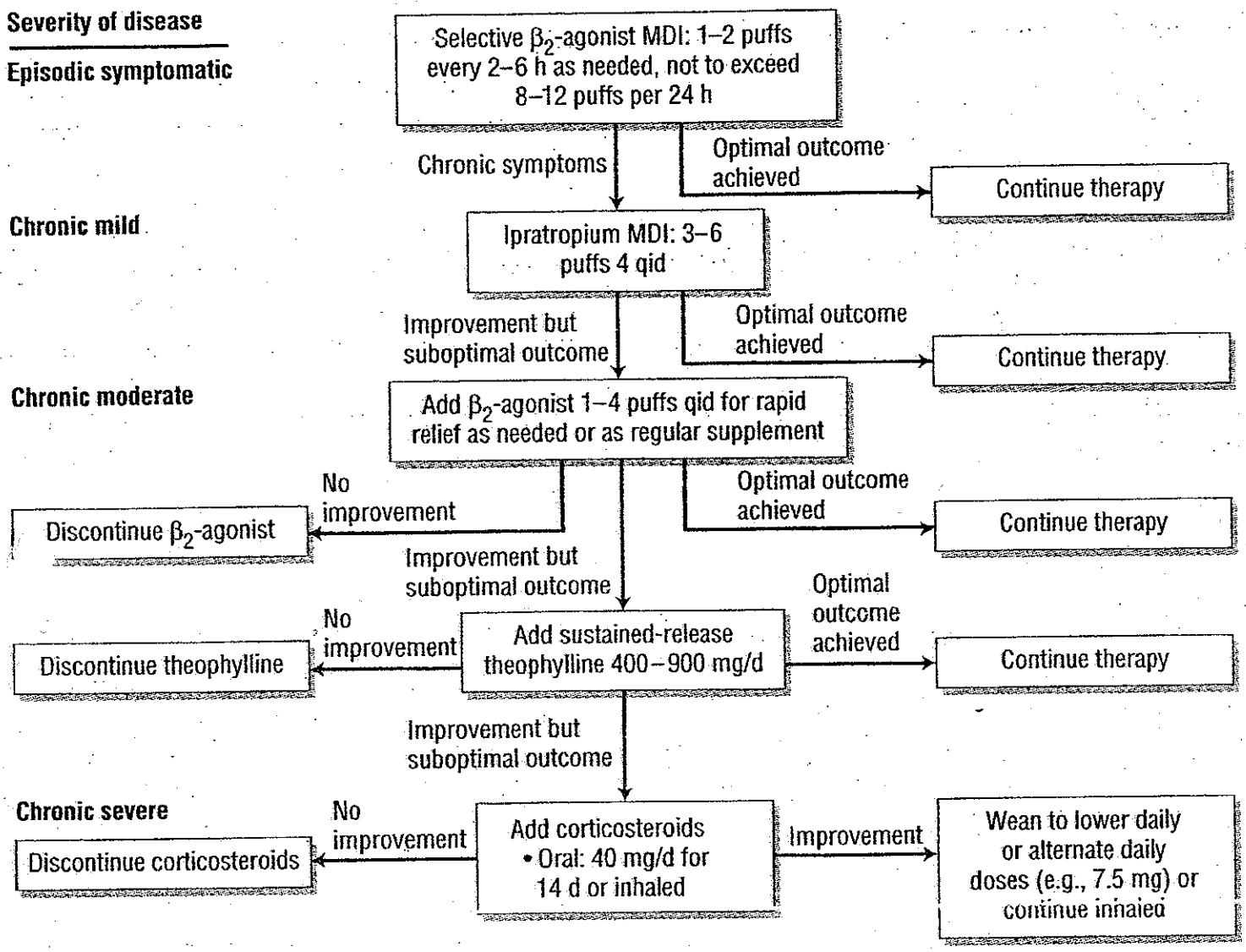
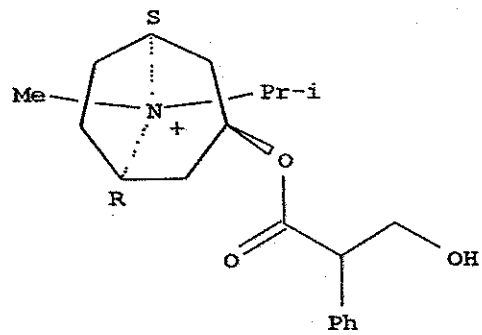


FIGURE 25–1. COLD treatment algorithm.

Tiotropium, a novel once-daily inhaled anticholinergic, has been shown to improve lung function over a 24-h period. In order to extend these findings, health-outcomes were evaluated over 1 yr in chronic obstructive pulmonary disease (COPD) patients. Spirometric results, peak expiratory flow rate (PEFR), salbutamol use and effects on dyspnea, health-related quality of life and COPD exacerbations were assessed in two identical 1-yr randomized double-blind double-dummy studies of tiotropium 18mg once daily (n=356) compared with ipratropium 40mg q.i.d. (n=179). Screening forced expiratory vol. in one second (FEV1) were 1.25±0.43 L (41.9±12.7% of the predicted value) (tiotropium) and 1.18±0.37 L (39.4±10.7% pred) (ipratropium). Trough FEV1 at 1 yr improved by 0.12±0.01 L with tiotropium and declined by 0.03±0.02 L with ipratropium ($p<0.001$). Significant improvement in PEFR, salbutamol use, Transition Dyspnea Index focal score, and the St George's Respiratory Questionnaire total and impact scores were seen with tiotropium ($p<0.01$). Tiotropium reduced the no. of exacerbations (by 24%, $p<0.01$), and increased time to first exacerbation ($p<0.01$) and time to first hospitalization for a COPD exacerbation ($p<0.05$) compared with ipratropium. Apart from an increased incidence of dry mouth in the tiotropium group, adverse events were similar between treatments. Tiotropium was effective in improving dyspnea, exacerbations, health-related quality of life and lung function in patients with chronic obstructive pulmonary disease, and exceeds the benefits seen with ipratropium. The data support the use of tiotropium once-daily as first-line maintenance treatment in patients with chronic obstructive pulmonary disease.

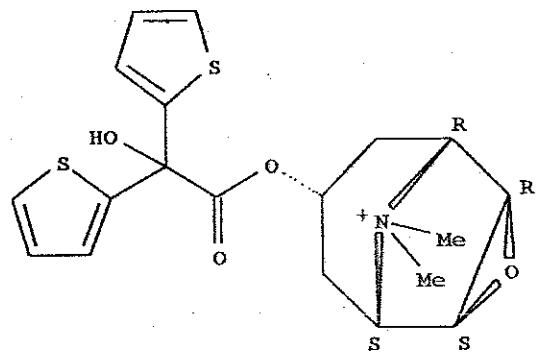
Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. Vincken, W.; van Noord, J. A.; Greefhorst, A. P. M.; Bantje, Th. A.; Kesten, S.; Korducki, L.; Cornelissen, P. J. G.; van de Bosch, J. M. M.; Dalinghaus, W. H.; Eland, M. E.; Evers, W. B. M.; Gans, S. J. M.; Gooszen, H. Ch.; Greefhorst, A. P. M.; van Harreveld, A. J.; van Kasteren, J. H. L. M.; Kuipers, A. F.; Nossent, G. D.; Pannekoek, B. J. M.; Pasma, H. R.; Peters, A.; Pieters, W. R.; Postmus, P. E.; Schreurs, A. J. M.; Sinninghe, H. E. J.; Sips, A. P.; van Spiegel, P. I.; Westbroek, J.; Aumann, J. L.; Janssens, E.; Pauwels, R.; Radermecker, M.; Slabbynck, H.; Stappaerts, I.; Verhaert, J.; Vermeire, P.; Vincken, W. Dutch/Belgian Tiotropium Study Group, Respiratory Division, Academic Hospital University of Brussels (AZ VUB), Brussels, Belg. European Respiratory Journal (2002), 19(2), 209-216.

Ipratropium



Antagoniste muscarinique non spécifique

Tiotropium



Antagoniste muscarinique M3

Le tiotropium est le premier membre d'une nouvelle classe thérapeutique, les anticholinergiques à longue durée d'action présentant une sélectivité cinétique pour les récepteurs muscariniques M3, principalement responsables de la bronchoconstriction. Le tonus vagal, qui provoque la contraction des muscles lisses des voies aériennes, constitue la majeure composante réversible de la bronchopneumopathie chronique obstructive (BPCO).

MUCOLYTIQUES

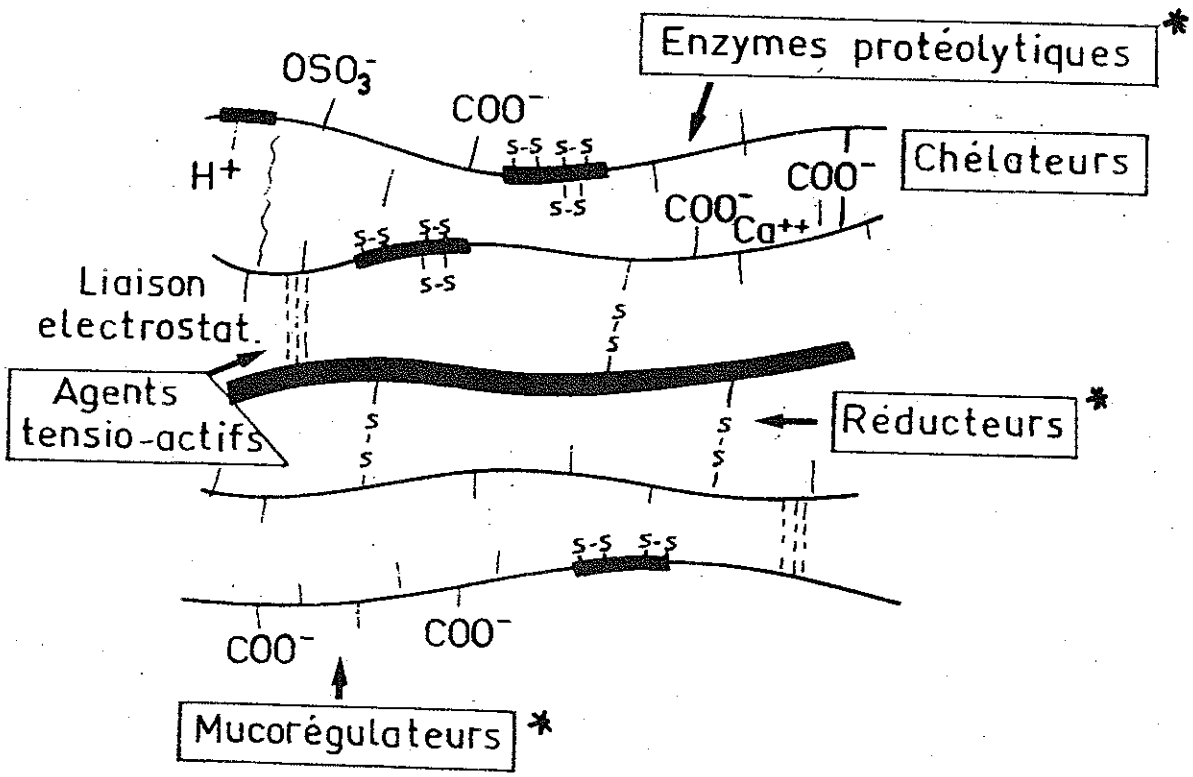
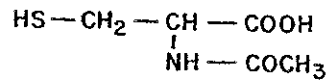


Fig. 5. Représentation schématique des glycoprotéines responsables de la structure fibrillaire du mucus bronchique. Principaux sites d'action des mucomodificateurs.

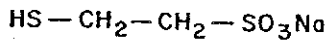
- Mucolytiques mais - réducteurs
  - agents protéolytiques
- Mucorégulateurs - actifs uniquement in vivo
- Hydratants (Tertémes)
- Bromhexine - action ? (clairance mucociliaire)
- ↑ de la sécrétion : fluorfénésine, KI, essenc. de thérébent. (stimulation vagale)

Dérivés de la cystéine

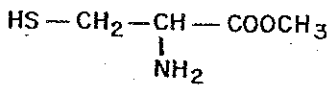
Groupe Thiol libre



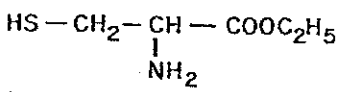
N-acétylcystéine



Mesna

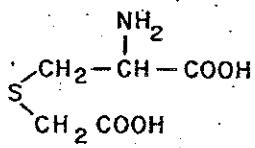


Mécystéine

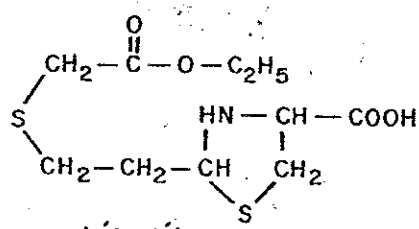


Ethylcystéine

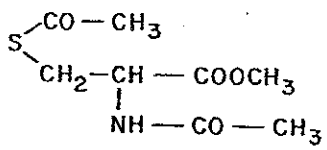
Groupe Thiol bloqué



Carbocystéine

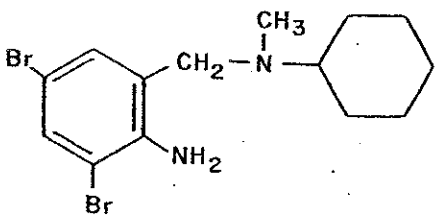


Létostéine



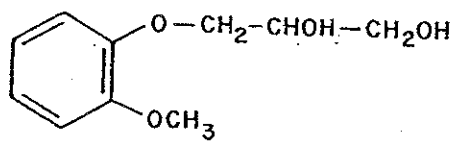
N-S-diacétylcystéinate de méthyle

Dérivés alcaloïdes



Bromhexine

Dérivés phénols



Guaïfénésine

Fig. 4. Formules chimiques développées des principaux mucomodificateurs.

TABLEAU I

Principales familles physicochimiques des mucomodificateurs

	Dénomination commune internationale	*Formule brute*	*Poids moléculaire*
Dérivés de la cystéine Groupe thiol libre	N—acétylcystéine	$C_5 H_9 O_3 NS$	163,2
	Mesna	$C_2 H_5 O_3 S_2 Na$	164,2
	Mécystéine	$C_4 H_{10} NS, HCl$	171,5
	Ethylcystéine	$C_5 H_{11} O_2 NS, HCl$	185,7
Groupe thiol bloqué	Carbocystéine	$C_5 H_9 O_4 NS$	179,2
	Létostéine	$C_{10} H_{17} O_4 NS_2$	279,4
	Mucothiol	$C_8 H_{13} N O_4 S$	219
Dérivés alcaloïdes	Bromhexine	$C_{14} H_{21} Br_2 N_2 Cl$	412,6
	Ambroxol	$C_{13} H_{12} Br_2 N_2 O, HCl$	
Dérivé de la pipérazine	Eprazinone	$C_{24} H_{34} N_2 O_2, Cl_2$	453,5
Dérivé des terpènes	Terpine	$C_{10} H_{20} O_2$	172,3
Dérivés des phénols	Guaïfénésine	$C_{10} H_{14} O_4$	198,2
	Guaïétoline	$C_{11} H_{16} O_4$	212
Enzymes protéolytiques	Serrapeptax	—	60 000
	Chymotrypsine	—	25 000
	Alpha-amylase	—	48 000
	Bromélaïnes	—	33 000
	Ribonucléase	—	—