

Use of mechanical ventilation in adults with severe asthma

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Asthma severe enough to require intubation and mechanical ventilation is associated with a mortality rate of about 10%. Therapeutic modalities are ever-changing and at times controversial. This paper provides an update on such modalities and presents, in a step-wise fashion, those most appropriate for practical patient care. The timing of intubation and the methods used to control airway patency, arterial pH and gas levels, and hemodynamic status are crucial to the success of therapy. Finally, conventional and disputed methods of bronchodilation are outlined.

Un taux de mortalité d'environ 10% est rattaché à l'asthme lorsque celui-ci est assez grave pour nécessiter intubation et ventilation mécanique. Les modalités de traitement changent continuellement et font parfois l'objet de controverse. Cet article fait le point sur les dernières modalités thérapeutiques et présente, étape par étape, celles qui sont les plus appropriées en matière de soins pratiques aux malades. Le moment choisi pour l'intubation, et les méthodes utilisées pour vérifier la liberté des voies respiratoires, le niveau du pH et des gaz artériels ainsi que l'état hémodynamique sont cruciaux pour le succès d'un traitement. Finalement, on expose les grandes lignes des méthodes conventionnelles ou contestées de bronchodilatation.

There have been many reviews of asthma therapy that have discussed immunotherapy, bronchodilating agents and the avoidance of precipitating factors. However, comparatively little has been written on the difficult and controversial management of an asthmatic patient in

respiratory failure who requires intubation and intermittent positive pressure ventilation (IPPV). The high and labile airway resistance in such patients necessitates a different approach than is used in those with predominantly chronic bronchitis or emphysema and a small amount of reversible airway obstruction. The mortality rate among patients with asthma who require IPPV is approximately 10%. However, it has been found to range from over 30% in older studies to 0% in some recent studies, presumably reflecting improvements in management.^{1,2}

We will discuss how to determine whether a patient with acute asthma requires IPPV and will offer a practical, stepwise approach to management once the decision to mechanically ventilate has been made.

Indications for IPPV

In patients with severe asthma, IPPV should be instituted when the risks of intubation and mechanical ventilation are judged to be less than those of continued conservative management. Our experience and a review of the current literature have provided guidelines for deciding whether to use mechanical ventilation. Frequent re-evaluation may be necessary, as the condition of patients with mild arterial blood-gas abnormalities may deteriorate quickly, whereas those with poor gas exchange may be alert and subsequently improve.³

The indications for IPPV are listed in Table I. However, no one factor is an absolute indication for IPPV. During an acute asthma attack the arterial carbon dioxide pressure (Paco₂) usually decreases owing to hyperventilation. However, when it increases to 40 mm Hg and there is no evidence of improvement the patient should be monitored closely in an intensive care facility, where an intra-arterial line can be inserted and prompt resuscitation is available. Although an elevated Paco₂ is an ominous sign, correlating with a forced expiratory volume

in 1 second (FEV₁) of less than 25%, Bondi and Williams⁸ found that of 27 asthmatic patients whose Paco₂ was greater than 40 mm Hg at the time of admission 23 did not require intubation. The average Paco₂ was 75 mm Hg in the patients who required ventilation, compared with 55 mm Hg in those who did not, but there was considerable overlap in the values.

It must be remembered that patients who require ventilation are often young, may never have been admitted to hospital before and are terrified. Repeated reassurance and explanations, especially regarding intubation, sedation and paralysis, are essential to alleviate fear and enhance cooperation.

Management with IPPV (Table II)

Intubation

Intubation of a patient with acute asthma entails considerable risk. Stimulation of the larynx and trachea may reflexively increase the bronchospasm, thereby aggravating the already severe hypoxemia and acidosis. The increase in airflow resistance may make subsequent venti-

Table I—Indications for intubation and mechanical ventilation

Clinical findings*
Diminished level of consciousness ⁴
Diminished response to pain ⁴
Progressive exhaustion ⁵
Absent breath sounds and wheezing ⁶
Fixed chest ⁶
Pulsus paradoxus ⁷
Arterial blood gas levels
pH less than 7.2
Carbon dioxide pressure
Increasing by more than 5 mm Hg/h ⁶
Greater than 55 to 70 mm Hg
Oxygen pressure less than 60 mm Hg ⁶
Evidence on chest x-ray films
Pneumothorax ⁷
Pneumomediastinum ⁷
Results of spirometric tests
Forced expiratory volume in 1 second less than 500 mL or vital capacity less than 1000 mL and failing to improve with bronchodilators ⁷

*Combined with decreasing arterial blood gas levels.

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lation extremely difficult. The procedure should therefore be performed by an experienced physician. The patient's blood pressure and cardiac rhythm must be monitored.

Although many premedication regimens are used, there are no published data that suggest which is best. However, in an alert patient the pharynx and larynx must be thoroughly anesthetized with lidocaine to minimize discomfort and inhibit bronchospasm. Thereafter, fast-acting sedatives with or without paralytic agents may be given immediately before intubation according to the patient's needs and depending on the premedication regimen with which the physician is most experienced.

One of us (P.W.M.) has found that the use of halothane simplifies intubation and is useful in the initial control of ventilation. Halothane is fast acting, it does not irritate the larynx, and its effect can be controlled. By dilating the bronchial smooth muscle it improves airflow, and by relaxing the skeletal muscles of the chest wall it increases compliance.⁹⁻¹¹ On the other hand, halothane impairs oxygenation and the elimination of carbon dioxide by the lungs, and, when combined with hypoxia, acidosis and mechanical airway stimulation, causes myocardial depression and increases myocardial irritability.⁹ However, these problems can be overcome by administering a very high concentration of inhaled oxygen and 100 mmol/L of sodium bicarbonate just before intubation.

A Portex endotracheal tube (Portex Inc., Scarborough, Ont.) 8 mm or more in diameter should be inserted nasally to provide comfort and tube stability and to aid suction. If nasal polyps are present intubation should be done orally to prevent severe epistaxis.

Control of ventilation

A volume-cycled respirator must be used to ensure that the tidal volumes remain constant while the airway pressures are high and fluctuating. Respiratory rates of 8 to 12/min usually allow adequate time for expiration and inhibition of further air-trapping in an already over-inflated lung. Low airflow rates re-

duce inspiratory pressures and ameliorate the adverse effect of the dependence of compliance on respiratory frequency, resulting in improved gas distribution and oxygenation. For adequate minute ventilation the tidal volumes should range from 10 to 12 mL/kg to allow the PaCO_2 to fall at a controlled rate.

Systemic fluid balance is very important during IPPV. High peak inflation pressures, which often range from 40 to 80 cm H_2O , may cause profound hypotension through reduced venous return if the patient is dehydrated. Excessive hydration must also be avoided since the amount of water in the lungs can theoretically be increased to deleterious levels in these patients.¹²

The use of positive end-expiratory pressure is generally considered to be contraindicated in patients with asthma because the functional residual capacity and peak inspiratory pressures are already high. However, there is no uniform agreement on this point. Qvist and colleagues¹³ believe that a positive end-expiratory pressure of up to 25 cm H_2O can combat air-trapping and thus recommend its use when conventional methods of management have not been successful.

If minute ventilation can easily be increased with IPPV, precipitous lowering of the PaCO_2 must be guarded against, as it may lead to alkalosis, with arrhythmias, seizures and increased bronchospasm.¹⁴ If, however, the high airway resistance limits effective minute ventilation, a low pH must be controlled with sodium bicarbonate until the bronchospasm begins to subside and the hypercapnia can be corrected.¹⁵

Maintenance of airway patency

For the maintenance of airway patency the patient's hands may initially have to be tied down to prevent self-extubation, a potentially fatal occurrence that complicates up to 13% of all intubations.¹⁶ The frequent suctioning required can increase the bronchospasm, but this problem can be overcome with the instillation of 40 mg of lidocaine in 5 to 10 mL of normal saline 5 minutes before suctioning. In vitro, lidocaine prevents muscle tissue from responding to various stimuli;¹⁷

specifically, it has been shown to prevent trachealis muscle contraction and mediator release in passively sensitized lungs of guinea pigs exposed to antigen.¹⁸

Bronchopulmonary lavage of secretions is extremely hazardous and has not been proven useful except in uncontrolled studies.^{6,19} Unless there is evidence of atelectasis due to proximal airway obstruction the benefits of this procedure are probably outweighed by the risks. It should therefore be done in conjunction with bronchoscopy and only when conventional measures have failed.

Sedation and paralysis

Large doses of a sedative are often required during mechanical ventilation. Patients are frightened and often uncooperative, and they cannot coordinate their breathing with the respirator; these factors result in a dangerously high inspiratory pressure and an inadequate tidal volume. Morphine is frequently used,²⁰⁻²² but we feel its use should be reconsidered. The use of opiates, including morphine and meperidine, can provoke histamine release, bronchospasm, vomiting, aspiration and

Table II—Aspects of management of an asthmatic patient requiring mechanical ventilation

Maintenance of airway patency
Large endotracheal tube
Hand restraints
Frequent suctioning
Ventilation
High tidal volumes
Low respiratory rate
Low airflow rates
Acid-base and fluid balance
Monitoring of central venous pressure
Replacement of glucose and potassium
Administration of sodium bicarbonate for severe acidosis
Sedation
Intravenous administration of diazepam
Paralysis
Intravenous administration of pancuronium bromide
Maximal bronchodilation
Salbutamol inhalation
Continuous aminophylline infusion
Methylprednisolone administration
Isoproterenol infusion
Halothane inhalation
Infection control
Repeated cultures
Treatment of identified infection
Extracorporeal membrane oxygenation
Repeated reassurance and explanations

drying of respiratory secretions, facilitating inspissation, and in large doses may cause seizures.⁹

We favour the use of diazepam because it relieves anxiety, causes hypnosis and indirectly relaxes the muscles of the chest wall, thus increasing compliance. Repeated doses of 5 to 10 mg administered intravenously cause minimal depression of blood pressure, cardiac output and ventricular stroke work, and the therapeutic:toxic dose ratio is high.⁹ Large doses are usually required to achieve the desired effect; Labrousse and coworkers²¹ suggested an average dose of 185 ± 177 mg.

Diazepam in large doses is frequently all that is required to control ventilation,²² but occasionally a neuromuscular blocking agent is required in addition.^{23,24} This approach permits synchronization of the patient's breathing with the ventilator, increases chest wall compliance and decreases total body oxygen consumption. We strongly favour pancuronium bromide because succinylcholine chloride and tubocurarine chloride cause histamine release, and gallamine triethiodide increases the blood pressure and heart rate.²⁴ Pancuronium, a bis-quaternary ammonium steroid synthesized in 1964, is a competitive neuromuscular blocking agent with no histamine-releasing action and minimal cardiovascular effects and ganglionic blocking action.²⁴ The effect of a single dose of 0.04 to 0.10 mg/kg is reversed in 20 minutes, although repeated doses accumulate with tissue saturation.

Bronchodilation

Beta-agonists, theophyllines and corticosteroids are the safest and most effective bronchodilators. It is therefore important to ensure optimal use of these conventional drugs in patients with worsening asthma, especially before more hazardous and unproven treatments are used.

For highly selective β_2 -agonists, such as salbutamol, inhalation is the preferred route of administration in terms of speed of onset, potency and lack of adverse systemic effects.^{25,26} While isoproterenol and salbutamol in equivalent inhaled doses produce a similar degree of bronchodilation, the latter has a longer duration of

action and is less likely to produce tremor and cardiovascular effects.²⁷ The intravenous route of administration is no more effective for salbutamol than the nebulized route, as judged by changes in the partial pressure of oxygen in arterial blood (P_{aO_2}) and the FEV_{10} , yet the former route more often causes untoward effects, such as tremor, agitation, tachycardia and ectopic beats.²⁸ Although the generally recommended single dose of nebulized salbutamol varies from 1.25 to 5.0 mg, the safe maximum dose is probably much higher. For example, Light and associates²⁷ proposed 10 mg as the optimal single dose. Higher doses produce progressive bronchodilation but only at the expense of more side effects. No serious adverse effects have been noted with 10 mg,^{27,28} but the actual amount of the drug that enters the respiratory tract is unknown and varies with the inhalational apparatus.

Isoproterenol produces 10 times the cardiac effect and 5 times the bronchodilator effect of salbutamol when given intravenously in equivalent doses.²⁰ Most experience with the use of isoproterenol in cases of severe asthma has been in children. Wood and collaborators²⁹ found that 27 of 35 children who would otherwise have undergone mechanical ventilation improved with intravenous doses of isoproterenol. However, Parry and colleagues³⁰ reported that 21% of the children in their study who had a P_{aCO_2} above 40 mm Hg and were treated with isoproterenol, 0.1 to 0.6 $\mu\text{g}/\text{kg} \cdot \text{min}^{-1}$, still required mechanical ventilation. They compared these findings with those in a historical control group of asthmatic children with a similar P_{aCO_2} who were not given isoproterenol: 19% of this group required mechanical ventilation. Whether the two groups matched in other characteristics affecting outcome is not known. Serious complications of treatment with isoproterenol are rare, and no drug-related deaths have been reported.^{1,30,31}

Although intravenously administered isoproterenol is a potent bronchodilator, it has not been adequately studied in adults with asthma. Complications may include cardiac arrhythmias and a transient fall in

the P_{aO_2} from pulmonary vasodilation, which will result in ventilation-perfusion mismatch. Its use would therefore be justified only in an asthmatic patient who has undergone mechanical ventilation but continues to worsen despite treatment with selective β -agonists, aminophylline and corticosteroids.

Aminophylline's effectiveness is dose-dependent in the therapeutic range, and the drug has considerable toxicity above this range. Therefore, a serum theophylline level between 44 and 100 $\mu\text{mol}/\text{L}$ (10 and 20 $\mu\text{g}/\text{mL}$) should be maintained at all times.³² In a patient who has not previously taken aminophylline a total loading dose of 6 mg/kg should be administered at a rate no greater than 0.2 mg/kg $\cdot \text{min}^{-1}$ and be followed by a constant infusion of 0.5 mg/kg $\cdot \text{h}^{-1}$.³² Frequent monitoring of the serum theophylline level is necessary since many factors may be present in asthmatic patients that alter the drug's disposition. For example, the use of erythromycin, cimetidine or oral contraceptives or the presence of a viral infection may reduce the rate of clearance. If the level is subtherapeutic it can quickly be corrected with an additional bolus that is half of the difference between the desired and actual serum concentrations as measured in micrograms per millilitre. If the level is too high the infusion should be discontinued in accord with the serum half-life, which, although highly variable, averages 5 to 6 hours.

Aminophylline has also been shown to increase the contractility and endurance of the diaphragm. This effect, which occurs in the therapeutic dose range, may prove to be of significant clinical benefit to the asthmatic patient with respiratory failure.³³

The underuse of corticosteroids has been implicated in the deaths of asthmatic patients,²³ yet the toxic effects of these agents are negligible.¹ Short-course corticosteroid therapy is considered safe even in the presence of infection.⁹ Methylprednisolone, which has approximately 125% the corticosteroid effect of prednisone when given in equal doses and less mineralocorticoid effect, with less resultant disturbance in the potassium and sodi-

um levels, is recommended in doses as high as 250 mg or greater, administered every 6 hours.³ Although no clinical trials have determined the highest effective dose of methylprednisolone, underuse is the real danger. One useful indicator of inadequate dosage is failure of the eosinophil count to fall below $50 \times 10^6/L$ within 36 hours.^{34,35}

Ipratropium bromide is a poorly absorbed derivative of atropine. Administered as a metered aerosol (40 µg per puff) it produces significant bronchodilation within 20 minutes and a maximum effect within 60 to 120 minutes.^{36,37} Its side effects appear to be minimal, unlike those of atropine, which include significant tachycardia, mydriasis and drying of respiratory secretions.³⁸ Whether ipratropium will prove to be a useful addition to the standard therapy we have outlined remains to be proven.

Halothane, with its bronchodilating effect, is another therapeutic tool for worsening asthma. Although not generally accepted management, the administration of 1% to 3% halothane has been used successfully in a few patients who have undergone mechanical ventilation and have not responded to more conservative therapy.^{10,11}

Although there have been reports of treatment with other bronchodilating agents, such as rectally administered ether and inhaled atropine, maximum effective use of β-agonists, aminophylline and corticosteroids, in conjunction with proper ventilation, sedation and paralysis, is usually all that is necessary for the successful management of patients who are undergoing mechanical ventilation.

In summary, a reasonable approach for aggressive bronchodilation includes the immediate administration of methylprednisolone in large doses, of aminophylline in doses high in the therapeutic range and of nebulized salbutamol, 2.5 to 10.0 mg every 2 to 3 hours, as indicated by the therapeutic response and the appearance of adverse effects. Only if the patient's condition continues to deteriorate does intervention with controversial measures become necessary in an attempt to prevent the patient's death. The intravenous use of isoproterenol given in increasing doses,

titrated according to the results of cardiac monitoring and the arterial blood gas levels seems justified. The use of halothane and selective bronchoscopic lavage would be final considerations.

Extracorporeal membrane oxygenation

If all forms of management fail to provide adequate gas exchange, or if serious barotrauma occurs, we suggest that the patient undergo extracorporeal membrane oxygenation (ECMO) until the disease process has been corrected. Asthmatic patients are ideal candidates for ECMO in that their disease process is reversible and they generally are young and have no underlying malignant disorder, bleeding diathesis or multisystem failure.

Conclusion

With optimal use of currently available therapeutic modalities the rate of death from asthma should continue to decline, even in patients with respiratory failure. However, in spite of changes in methods of critical care, it is likely that preventive care has the greatest potential to decrease the rates of illness and death in asthma since most patients can easily be treated by an interested and informed physician. Although in a few patients the asthma is highly labile and accompanied by rapid-onset respiratory failure, most admissions to hospital for status asthmaticus are thought to be preventable.^{3,22} Once the life-threatening situation has passed, the most important aspects of management — education, medication and close follow-up — must begin.

References

1. RICHARDS W, LEW C, CARNEY J, PLATZKER A, CHURCH JA: Review of intensive care unit admissions for asthma. *Clin Pediatr (Phila)* 1979; 18: 345-352
2. JAMES OF, MILLS RM, ALLEN KM: Severe bronchial asthma: factors influencing intensive care management and outcome. *Anaesth Intensive Care* 1977; 5: 11-18
3. PETTY TL, SCOGGIN CH: Therapeutic considerations in status asthmaticus. *J Am Med Assoc* 1977; 32: 395-404
4. WOOD DW, DOWNES JJ, LECKS HI: The management of respiratory failure in childhood status asthmaticus. Experience

- with 30 episodes and evolution of a technique. *J Allergy* 1968; 42: 261-287
5. BIERMAN CW, PIERSON WE, SHAPIRO GG: Treatment of status asthmaticus in children. *South Med J* 1975; 68: 1556-1560
6. SCHULANER FA, MATTIKOW MS: Treatment of status asthmaticus: bronchial asthma — part III. *J Med Soc NJ* 1980; 77: 501-505
7. REBUCK AS, READ J: Assessment and management of severe asthma. *Am J Med* 1971; 51: 788-798
8. BONDI E, WILLIAMS MH JR: Severe asthma: course and treatment in hospital. *NY State J Med* 1977; 77: 350-353
9. JAFFE JH, MARTIN WR: Opioid analgesics and antagonists. In GILMAN AG, GOODMAN LS, GILMAN A (eds): *The Pharmacological Basis of Therapeutics*, 6th ed, Macmillan, New York, 1980: 494-534
10. GÓMEZ GÓMEZ M, GARCÍA AGUILAR L, MOZO BARRALES A, PALACIOS TREVINO JL: Halothane: un recurso más en el paciente en estado de mal asmático. *Bol Med Hosp Infant Mex* 1980; 37: 355-358
11. O'ROURKE PP, CRONE RK: Halothane in status asthmaticus. *Crit Care Med* 1982; 10: 341-343
12. BAKER JW, YERGER S, SEGAR WE: Elevated plasma antidiuretic hormone levels in status asthmaticus. *Mayo Clin Proc* 1976; 51: 31-34
13. QVIST J, ANDERSEN JB, PEMBERTON M, BENNIKE KA: High-level PEEP in severe asthma (C). *N Engl J Med* 1982; 307: 1347-1348
14. SCOGGIN CH: Acute asthma in adults. *Compr Ther* 1979; 5 (3): 8-13
15. MENITOVE SM, GOLDRING RM: Combined ventilator and bicarbonate strategy in the management of status asthmaticus. *Am J Med* 1983; 74: 898-901
16. STAUFFER JL, OLSON DE, PETTY TL: Complications and consequences of endotracheal intubation and tracheotomy. A prospective study of 150 critically ill adult patients. *Am J Med* 1981; 70: 65-76
17. WEISS EB, HARGRAVES WA, VISWANATH SG: The inhibitory action of lidocaine in anaphylaxis. *Am Rev Respir Dis* 1978; 117: 859-869
18. WEISS EB, ANDERSON WH, O'BRIEN KP: The effect of a local anesthetic, lidocaine, on guinea pig trachealis muscle in vitro. *Am Rev Respir Dis* 1975; 112: 393-400
19. SCOGGIN CH, SAHN SA, PETTY TL: Status asthmaticus; a nine-year experience. *JAMA* 1977; 238: 1158-1162
20. SHEEHY AF, DiBENEDITTO R, LEFRAK S, LYONS HA: Treatment of status asthmaticus. *Arch Intern Med* 1972; 130: 37-42
21. LABROUSSE J, BOUSSER AP, TENAILLON A, MORGANT C, LISSAC J: Traitement de l'état de mal asthmatique. *Therapie* 1977; 32: 49-61
22. SIMONS FE, PIERSON WE, BIERMAN CW: Respiratory failure in childhood status asthmaticus. *Am J Dis Child* 1977; 131: 1097-1101

23. WESTERMAN DE, BENATAR SR, POTGIETER PD, FERGUSON AD: Identification of the high-risk asthmatic patient. Experience with 39 patients undergoing ventilation for status asthmaticus. *Am J Med* 1979; 66: 565-572
24. LEVIN N, DILLON JB: Status asthmaticus and pancuronium bromide. *JAMA* 1972; 222: 1265-1268
25. SIMPSON H, MITCHELL I, INGLIS JM, GRUBB DJ: Severe ventilatory failure in asthma in children; experience of 13 episodes over 6 years. *Arch Dis Child* 1978; 53: 714-721
26. SHIM C, WILLIAMS MH JR: Bronchial response to oral versus aerosol metoprolol in asthma. *Ann Intern Med* 1980; 93: 428-431
27. LIGHT RW, TAYLOR RW, GEORGE RB: Albuterol and isoproterenol in bronchial asthma; efficacy and toxicity of drugs administered via intermittent positive pressure breathing. *Arch Intern Med* 1979; 139: 639-643
28. LAW FORD P, JONES BJM, MILLEDGE JS: Comparison of intravenous and nebulised salbutamol in initial treatment of severe asthma. *Br Med J* 1978; 1: 84
29. WOOD DW, DOWNES JJ, SCHEINKOPF H, LEEKS HI: Intravenous isoproterenol in the management of respiratory failure in childhood status asthmaticus. *J Allergy Clin Immunol* 1972; 50: 75-81
30. PARRY WH, MARTORANO F, COTTON EK: Management of life-threatening asthma with intravenous isoproterenol infusions. *Am J Dis Child* 1976; 130: 39-42
31. COTTON EK, PARRY W: Treatment of status asthmaticus and respiratory failure. *Pediatr Clin North Am* 1975; 22: 163-171
32. POWELL JR, VOZEH S, HOPEWELL P, COSTELLO J, SHEINER LB, RIEGELMAN S: Theophylline disposition in acutely ill hospitalized patients. The effect of smoking, heart failure, severe airway obstruction and pneumonia. *Am Rev Respir Dis* 1978; 118: 229-238
33. AUBIER M, DE TROYER A, SAMPSON M, MACKLEM PT, ROUSSOS C: Aminophylline improves diaphragmatic contractility. *N Engl J Med* 1981; 305: 249-252
34. HORN BR, ROBIN ED, THEODORE J, VAN KESSEL A: Total eosinophil counts in the management of bronchial asthma. *N Engl J Med* 1975; 292: 1152-1155
35. LOWELL FC: The total eosinophil count in obstructive pulmonary disease (E). *Ibid*: 1182-1183
36. REBUCK AS, CHAPMAN KR, BRAUDE C: Anticholinergic therapy of asthma. *Chest* 1982; 82 (suppl 1): 55S-57S
37. BRUDERMAN I, COHEN-ARONOVSKI R, SMORZIK J: A comparative study of various combinations of ipratropium bromide and metoprolol in allergic asthmatic patients. *Chest* 1983; 83: 208-210
38. RUFFIN RE, WOLFF RK, DOLOVICH MB, ROSSMAN CM, FITZGERALD JD, NEWHOUSE MT: Aerosol therapy with Sch 1000. Short-term mucociliary clearance in normal and bronchitic subjects and toxicology in normal subjects. *Chest* 1978; 73: 501-506

Prescribing Information

Lopresor® (metoprolol tartrate)

50 mg and 100 mg tablets
200 mg slow-release tablets

Therapeutic Classification

Antihypertensive and anti-anginal agent.

Actions

Metoprolol tartrate is a beta-adrenergic-receptor-blocking agent with predominant blocking effect on beta₁ receptors.

Indications

a) Mild and Moderate Hypertension:

Usually used in combination with other drugs, particularly a thiazide diuretic, however, may be tried alone as an initial agent in those patients whose treatment should be started with a beta-blocker rather than a diuretic. The combination of Lopresor with a diuretic or peripheral vasodilator has been found to be compatible and generally more effective than Lopresor alone. Incompatibility with other antihypertensive agents has not been found, experience is limited however. Not recommended for the emergency treatment of hypertensive crises.

b) Angina Pectoris

Lopresor is indicated in patients with angina pectoris due to ischemic heart disease.

Contraindications

Sinus bradycardia, second and third degree A-V block, right ventricular failure secondary to pulmonary hypertension, congestive heart failure, cardiogenic shock, anesthesia with agents that produce myocardial depression, e.g. ether and chloroform.

Warnings

a) **Cardiac Failure:** Special caution should be exercised when administering Lopresor to patients with a history of heart failure, since inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients without a history of cardiac failure, continued depression of the myocardium can lead to cardiac failure. At the first sign of impending cardiac failure, patients should be digitalized and/or given a diuretic and observed closely.

Lopresor does not abolish the inotropic action of digitalis on the heart muscle, however, the positive inotropic action of digitalis may be reduced by the negative inotropic effect of Lopresor when the two drugs are used concomitantly. The effects of beta-blockers and digitalis are additive in depressing A-V conduction. If cardiac failure continues, despite adequate digitalization and diuretic therapy, discontinue Lopresor therapy.

b) **Abrupt Cessation of Therapy with Lopresor:** Warn patients against abrupt discontinuation. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias in patients with angina following abrupt discontinuation of beta-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. When discontinuation of Lopresor is planned in patients with angina, dosage should be gradually reduced over a period of about two weeks and the patient carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, Lopresor should be discontinued stepwise, under conditions of closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with Lopresor be reinstated promptly, at least temporarily.

c) Various skin rashes and conjunctival xerosis have been reported. A severe syndrome (oculo-muco-cutaneous syndrome) whose signs include conjunctivitis sicca and psoriasisiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-adrenergic-blocking agent (practolol) but has not been observed with Lopresor or any other such agent. Physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

d) Severe sinus bradycardia may occur, in such cases, dosage should be reduced.

e) Lopresor may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of Lopresor may be followed by an exacerbation of the symptoms of hyperthyroidism including thyroid storm.

Precautions

a) Careful monitoring of patients with diseases associated with bronchospasm is mandatory and a bronchodilator must be administered concomitantly.

b) Administer with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia.

c) Adjust dosage individually when used concomitantly with other anti-hypertensive agents.

d) Closely monitor patients also receiving catecholamine-depleting drugs, such as reserpine or guanethidine. Lopresor should not be combined with other beta-blockers.

e) Appropriate laboratory tests should be performed at regular intervals during long-term treatment.

f) Lopresor should not be given to patients receiving verapamil. In exceptional cases, when in the opinion of the physician concomitant use is considered essential, such use should be instituted gradually, in a hospital setting, under careful supervision.

g) **In patients undergoing elective or emergency surgery:** Lopresor should be withdrawn gradually following recommendation given under Abrupt Cessation of Therapy (see WARNINGS). Available evidence suggests that the clinical and pharmacological effects of beta-

blockade induced by Lopresor are no longer present 48 hours after cessation of therapy.

In emergency surgery, effects of Lopresor may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or levaterenol.

h) **Usage in pregnancy and nursing mothers:** Lopresor crosses the placental barrier and appears in breast milk. It should not be given to pregnant women as it has not been studied in human pregnancy. If use of the drug is deemed essential in nursing mothers, the patient should stop nursing.

i) **Usage in children:** There is no experience with Lopresor in the pediatric age groups.

Adverse reactions

Cardiovascular: Congestive heart failure (see WARNINGS), secondary effects of decreased cardiac output which include: syncope, vertigo, lightheadedness and postural hypotension; severe bradycardia, lengthening of PR interval, second and third degree A-V block, sinus arrest, palpitations, chest pains, cold extremities, Raynaud's phenomenon, claudication, hot flushes.

Central Nervous System: headache, dizziness, insomnia, mental depression, lightheadedness, anxiety, tinnitus, weakness, sedation, vivid dreams, vertigo, paresthesia.

Gastrointestinal: diarrhea, constipation, flatulence, heartburn, nausea and vomiting, abdominal pain, dryness of mouth.

Respiratory: shortness of breath, wheezing, bronchospasm, status asthmaticus.

Allergic/Dermatological (see WARNINGS): exanthema, sweating, pruritus, psoriasisiform rash.

EENT: blurred vision and non-specific visual disturbances, itching eyes.

Miscellaneous: tiredness, weight gain, decrease in libido. **Clinical Laboratory:** The following laboratory parameters have been rarely elevated: transaminases, BUN, alkaline phosphatase and bilirubin. Thrombocytopenia and leucopenia have been reported rarely.

Symptoms and Treatment of Overdosage

Symptoms: bradycardia, congestive heart failure, hypotension, bronchospasm, hypoglycemia.

Treatment: Discontinue Lopresor and observe patient closely. In addition, if required, the following therapeutic measures are suggested.

1. Bradycardia, and hypotension:

Initially 1-2 mg of atropine sulfate should be given intravenously. If a satisfactory effect is not achieved, a pressor agent such as norepinephrine may be administered after preceding treatment with atropine.

2. Heart Block: (second or third degree)

Isoproterenol or transvenous cardiac pacemaker.

3. Congestive heart failure:

Conventional therapy.

4. Bronchospasm:

Aminophylline or a beta₂-agonist.

5. Hypoglycemia:

Intravenous glucose.

Large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of Lopresor.

However, the complications of excess isoproterenol, e.g. hypotension and tachycardia, should not be overlooked.

Dosage and Administration

a) **Hypertension:** Initial Dose: 50 mg b.i.d. If adequate response is not seen after one week, dosage should be increased to 100 mg b.i.d. In some cases the daily dosage may need to be increased by further 100 mg increments at intervals of not less than two weeks up to a maximum of 200 mg b.i.d., which should not be exceeded.

Usual Maintenance Dose: 150-300 mg daily.

When combined with another antihypertensive agent which is already being administered, Lopresor should be added initially at a dose of 50 mg b.i.d. After 1 or 2 weeks the daily dosage may be increased if required, in increments of 100 mg, at intervals of not less than 2 weeks, until adequate blood pressure control is obtained.

b) **Angina pectoris:** Initial Dosage: 50 mg b.i.d. for the first week. If response is not adequate, the daily dosage should be increased by 100 mg for the next week. The need for further increases should be closely monitored at weekly intervals and the dosage increased in 100 mg increments to a maximum of 400 mg/day in 2 or 3 divided doses.

Usual Maintenance Dosage: 200 mg/day.

Dosage Range: 100-400 mg per day in divided doses.

A dose of 400 mg/day should not be exceeded.

c) **Slow-release Lopresor SR 200 mg:** Lopresor SR 200 mg is intended only for maintenance dosing in those patients requiring doses of 200 mg per day.

Treatment must always be initiated and individual titration of dosage carried out using the regular tablets.

Patients with hypertension or angina pectoris on a maintenance regimen of one 100 mg tablet twice daily may be changed to one Lopresor SR 200 mg tablet taken in the morning.

Lopresor SR 200 mg tablets should be swallowed whole.

Availability

Lopresor

Tablet: 50 mg:

Film coated, light red, capsule-shaped tablet, embossed 51 and scored on one side and GEIGY on the other.

Tablet: 100 mg:

Film coated, light blue, capsule-shaped tablet, embossed 71 and scored on one side and GEIGY on the other.

Lopresor SR

Slow-release Tablet: 200 mg:

Film-coated, light yellow, round tablet, embossed GEIGY on one side and CDC on the other.

Product monograph supplied on request.



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Geigy

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