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Question: What is the difference between Volmax[®] and Proventil Repetabs[®]?

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Repetabs®?

Comments

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Question: What is the difference between Volmax® and Proventil Repetabs®?

BY JEFFERY A. GOAD, ROBERT ANDONIAN, CHRIS CHANG AND GREG THOMPSON, PHARM.D.

Answer: There are noticeable differences between Volmax and Proventil Repetabs, two of the available oral forms of administering albuterol to patients suffering from asthma. These differences are discussed below.

Mechanism of action

Albuterol is a beta-2 selective adrenergic receptor agonist with minimal beta-1 adrenergic receptor activity that has been used extensively to prevent and treat reversible obstructive airway disease. Beta-adrenergic agonists stimulate the adenylylase enzyme which catalyzes the formation of cyclic-3'5' adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). The cAMP formed mediates the cellular response thought to be responsible for bronchodilation. The resultant relaxation of bronchial smooth muscle relieves bronchospasm and reduces airway resistance.

Delivery system

Volmax extended-release tablets deliver albuterol by utilizing the oral osmotic drug delivery system (OROS® system). Each tablet consists of nondeformable, inert, semi-permeable material that

serves as the rate-controlling membrane. The membrane is punctured by a minute, 250 micrometer-diameter laser-drilled hole. Sodium chloride is the osmotic agent responsible for the influx of water into the core. The release rate of Volmax extended-release tablets depends on the rate of fluid influx. Approximately 90 percent of the albuterol dose is released over the initial eight hours, while the remainder of the drug is released over the next two hours.¹

Proventil Repetabs tablets are formulated to provide a duration of action up to 12 hours by utilizing an outer coating and a barrier/protective core method. The outer coating consists of 2 mg of albuterol available for immediate release. The remainder of albuterol within the core is released four to six hours later.²

Comparative clinical pharmacokinetics

There have been several well-designed studies in patients with asthma to compare the pharmacokinetics of Volmax and Proventil Repetabs (Table 1). Researchers compared the steady-state pharmacokinetics of Volmax (8 mg every 12 hours) and Proventil Repetabs (two 4 mg tablets every 12 hours). Volmax demonstrated

significantly less absolute and relative peak-trough fluctuation during both daytime and nighttime dosing intervals, as compared with Proventil Repetabs. Also, Volmax provides more consistent plasma albuterol concentrations consistent with the OROS delivery system. Proventil Repetabs' peak plasma concentrations were higher and occurred earlier due to their unique release system.³

Several studies showed no significant difference between the two extended-release 4 mg formulations in terms of C_{max} reduction due to the presence of food. The T_{max}, though, occurred significantly later during the fed treatment for Volmax (4.9 hours fasted versus 6.4 hours fed; p < .01). No differences were observed in the area under the plasma concentration-time curve (AUC) for either formulation under fasting versus fed conditions. Food does not change the amount of albuterol that is absorbed from either Volmax or Proventil Repetabs, but it does delay the onset and the rate of absorption for both products. These results indicate that food may slow the rate of absorption of albuterol from both products, but the extent of absorption is not affected.⁴

Clinical implications

With over 20 years of experience using Proventil Repetabs, do we really need another sustained-release albuterol preparation? The answer may be yes, considering Volmax's lower cost and smoother pharmacokinetic profile.

Proventil Repetabs' release mechanism is a pH-dependent, two-phase system. Consequently, albuterol is released in a bimodal fashion with two peaks. The double-peaking action is proposed to be responsible for the observed increase in interpatient bronchodilatory response between the two products. The clinical effects of this finding are unclear, as there were no statistical differences in pulmonary function tests (FEV₁, FEF and FVC)

TABLE 1

Pharmacokinetics of Volmax and Proventil Repetabs

Parameters	Proventil Repetabs® (two 4 mg tablets)	Volmax® 8mg Extended Release Tablet
Delivery System	2 phase pH-dependent release	OROS® (oral osmotic system)
AUC	Day: 117 ng hr/ml; Night: 110 ng hr/ml	Day: 114 ng hr/ml; Night: 103 ng hr/ml
T _{1/2} (steady state)	5-6 hours	9.3 hours
C _{max} (nighttime)	12.2 ng/ml	10.9 ng/ml
C _{min} (nighttime)	7.2 ng/ml	7.4 ng/ml
T _{max} (nighttime)	4.7 hours	7.3 hours
Peak-Trough Flux (relative)	0.6	0.4
Coefficient of FEV ₁ Variation	167%	89%

Muro Pharmaceutical Inc. Product Information, 1994.

between the two groups at any time during the study. The study looked at a treatment course of one to seven days and found variations in pharmacokinetic data only. The side effect profiles also were not significantly different.

Although clinical outcomes of pulmonary function do not support Volmax as superior to Proventil Repetabs, it is reasonable to assume that an ideal sustained-release system should release a constant amount of drug over a given interval. Volmax achieves a constant rate of release through a non-pH-dependent mechanism. Since an important niche for these oral beta-2 agonists is in the prevention of nocturnal asthma, consistent bronchodilation may be important. Volmax did demonstrate less interpatient variability over the dosing interval compared to Proventil Repetabs.⁵

Finally, cost is an ever-important issue when deciding which drug to choose. After determinations of safety and effi-

cacy are assured, one must consider cost of treatment. Using the manufacturers' recommendation of 8 mg twice daily for Volmax and two 4 mg Proventil Repetabs twice daily, the AWP of Volmax is somewhat less than Proventil Repetabs. As important formulary decisions are made concerning the fate of these oral beta agonists, Volmax should be a welcome newcomer to the minds and budgets of pharmacists.

About the authors

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