Clinical Pharmacokinetics of Bambuterol

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Summary

Bambuterol, a biscarbamate ester prodrug of the β2 adrenergic agonist terbutaline, has been approved for the treatment of asthma in 28 countries. It is available in 10 and 20mg (25 and 50 μmol) tablets as the hydrochloride salt.

Bambuterol is stable to presystemic elimination and is concentrated by lung tissue after absorption from the gastrointestinal tract. The prodrug is hydrolysed to terbutaline primarily by butyrylcholinesterase, and lung tissue is capable of this metabolic pathway. It is also oxidatively metabolised to products which can be hydrolysed to terbutaline.

Peak terbutaline plasma concentrations occur 3.9 to 6.8 hours after bambuterol ingestion, and the peak : trough terbutaline concentration ratio is lower than that after ingestion of terbutaline. Older patients have a greater area under the plasma concentration-time curve for terbutaline over a dose interval at steady-state.

Whether genetic variations in the expression of butyrylcholinesterase alter therapeutic response remains to be determined. The efficacy of bambuterol has been demonstrated to last for 24 hours after ingestion; once-daily administration in the evening is recommended. Maximum therapeutic benefit requires more than 1 week of treatment.
Except for the suppression of plasma butyrylcholinesterase, the adverse effect profile of bambuterol is essentially that of a \( \beta_2 \) agonist and is best correlated with circulating terbutaline concentration in plasma. Plasma butyrylcholinesterase activity returns to control values approximately 2 weeks after discontinuation of treatment with bambuterol.

This new drug provides oral \( \beta_2 \) agonist therapy in a more convenient form than was available previously, and may have a better therapeutic : toxic ratio than terbutaline.

Bambuterol is a biscarbamate ester prodrug of the \( \beta_2 \) adrenergic agonist terbutaline. It has been approved for the treatment of asthma in 28 countries, including the UK, Germany, Sweden, Italy, Spain and Canada.

1. Chemical Properties and Formulation

Bambuterol (1-[3,5-bis(N,N-dimethylcarbamoyloxy)phenyl]-2-t-butylaminoethanol hydrochloride) [Bambec\(^\circ\)] is a racemic product with a single chiral centre at the carbon side-chain position alpha on the aromatic ring (fig. 1).\(^1\) It was designed as an ester prodrug of terbutaline, demonstrating hydrolytic stability, an affinity for lung tissue, relative stability to presystemic metabolism, and relative specificity for hydrolysis by butyrylcholinesterase (liberating terbutaline).\(^2\) The drug is formulated as the hydrochloride salt in 10mg and 20mg tablets.

2. Mechanism of Activation

Bambuterol is a prodrug that must be hydrolysed to terbutaline, the active \( \beta_2 \) adrenergic receptor agonist. Hydrolysis to terbutaline has been demonstrated in blood samples from humans and laboratory animals.\(^3,4\) The mechanism appears to be enzymatic, with the major enzyme identified as butyrylcholinesterase for both bambuterol and its monocarbamate metabolite. The mechanism was shown to be noncompetitive, bambuterol being 10 times more potent than the monocarbamate metabolite.\(^3\) Physostigmine completely inhibits the rapid early hydrolysis reaction in human blood, but only modestly inhibits the slow hydrolysis phase.\(^4\)

The selectivity of bambuterol for butyrylcholinesterase is such that toxicity related to the inhibition of acetylcholinesterase was considered unlikely with therapeutic use of the drug.\(^3\) These investigators also report that bambuterol and the monocarbamate metabolite retard their own hydrolysis to terbutaline by butyrylcholinesterase, and therefore prolong the duration of action of an ingested dose. The ability of bambuterol to inhibit butyrylcholinesterase is dependent upon the genetic variant of this enzyme, and shows a trimodal distribution. The normal enzyme is most easily inhibited, with the heterozygous form showing intermediate susceptibility, and the atypical form being the least sensitive to inhibition by bambuterol.\(^5\) It remains to be proven whether patients with heterozygous or atypical butyrylcholinesterase have a different therapeutic response to that of patients with the normal enzyme.

Studies of the pharmacological effects of terbutaline in animals have shown its relatively modest effects on the heart, circulation and CNS, relative to its pronounced bronchodilator activity.\(^6\) Its

![Fig. 1. Structure of bambuterol (free base). Shaded areas represent the carbamic acid ester substituents, which are hydrolysed by butyrylcholinesterase, leaving the \( \beta_2 \) receptor agonist terbutaline (reproduced from Sitar et al.,\(^1\) with permission).](image)