Verapamil: A Review of its Pharmacological Properties and Therapeutic Use

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Verapamil: A Review

Summary

Synopsis: Verapamil\textsuperscript{2} is a novel antiarrhythmic and antianginal agent which, although introduced in 1962, has only recently gained prominence not only as a significant agent in cardiovascular therapeutics but also as a powerful tool to examine the nature of some of the biophysical phenomena at the membrane of cardiac and other excitable tissues. Verapamil is the prototype of those agents which selectively inhibit membrane transport of calcium, an action which accounts for the drug's peripheral and coronary vasodilator properties, its effect on excitation-contraction coupling and hence its negative inotropic propensity, as well as its depressant effects on the sinus node and atrioventricular conduction. Its pharmacological effects are largely independent of the autonomic nervous system. The main therapeutic uses of the drug are in the management of atrial tachyarrhythmias, angina, and possibly hypertension. The overall experimental and clinical data suggest that verapamil will become an important and safe addition to existing drug regimens, especially as an agent of choice for the short-term treatment of most cases of paroxysmal supraventricular tachycardias. The initial experience in other arrhythmias, angina and hypertension, is also sufficiently encouraging to justify further detailed clinical trials to define its potential role in cardiovascular therapeutics.

Pharmacodynamic Properties: Verapamil is a weak local anaesthetic; it does not depress the upstroke velocity of the cardiac action potential, nor does it prolong the action potential duration in heart muscle. It selectively depresses nodal tissues, presumably by an effect on the calcium-mediated slow response, an action distinct from that of all other antiarrhythmic agents.

Pharmacokinetics: Preliminary pharmacokinetic studies reveal major discrepancies between the duration of the electrophysiological and haemodynamic effects of verapamil and the presence of unchanged drug in the plasma, raising the possibility of active metabolites. Plasma protein binding of verapamil approaches approximately 90%. Despite almost complete gastrointestinal absorption following oral administration, the overall bioavailability of the drug is about 10 to 22% reflecting substantial first pass hepatic metabolism which may account for the 8 to 10-fold greater oral compared with intravenous doses needed to produce comparable pharmacodynamic effects.

Therapeutic Trials: The antiarrhythmic effects of verapamil are explained largely by its action on the atrioventricular node: intravenously administered verapamil (10mg in adults, 3.5 to 5mg in children) produces prompt reversion to sinus rhythm of 80 to 100% of cases with paroxysmal supraventricular tachycardias, especially those due to AV nodal re-entry. The drug has little effect on the anomalous pathways in the Wolff-Parkinson-White syndrome so that atrial fibrillation or flutter complicating this disorder are not affected by verapamil, in contrast to other cases of atrial fibrillation or flutter in which the ventricular response is consistently reduced in most cases and sinus rhythm restored in a few. The role of oral verapamil used alone or in combination with other agents in the prophylaxis of paroxysmal supraventricular tachycardias and in the maintenance of sinus rhythm following cardioversion of atrial fibrillation remains to be defined. Verapamil is of little value in the control of ventricular arrhythmias.

Verapamil is also effective in angina pectoris in doses in excess of 120mg 3 times daily orally. At this dose schedule, its efficacy is comparable with that of 80mg 3 times daily of oral propranolol, although the latter produces a significant degree of bradycardia whereas verapamil does not. The mode of antianginal action of verapamil is therefore not understood, but unlike propranolol the drug has no effects on lung function. Experimental studies suggest that verapamil might reduce myocardial infarct size and preliminary clinical studies raise the possibility that the drug may be of value in the management of acute hypertensive crisis as well as of treatment of essential hypertension.

\textsuperscript{2} Isoptin (Knoll AG), Cordilox (Abbott).