

Cardiac electrophysiologic and antiarrhythmic actions of a pavine alkaloid derivative, *O*-methyl-neocaryachine, in rat heart

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1 *O*-methyl-neocaryachine (OMNC) suppressed the ischaemia/reperfusion-induced ventricular arrhythmias in Langendorff-perfused rat hearts ($EC_{50}=4.3 \mu M$). Its electrophysiological effects on cardiac myocytes and the conduction system in isolated hearts as well as the electromechanical effects on the papillary muscles were examined.

2 In rat papillary muscles, OMNC prolonged the action potential duration (APD) and decreased the maximal rate of depolarization (V_{max}). As compared to quinidine, OMNC exerted less effects on both the V_{max} and APD but a positive inotropic effect.

3 In the voltage clamp study, OMNC decreased Na^+ current (I_{Na}) ($IC_{50}=0.9 \mu M$) with a negative-shift of the voltage-dependent inactivation and a slowed rate of recovery from inactivation. The voltage dependence of I_{Na} activation was, however, unaffected. With repetitive depolarizations, OMNC blocked I_{Na} frequency-dependently. OMNC blocked I_{Ca} with an IC_{50} of $6.6 \mu M$ and a maximum inhibition of 40.7%.

4 OMNC inhibited the transient outward K^+ current (I_{to}) ($IC_{50}=9.5 \mu M$) with an acceleration of its rate of inactivation and a slowed rate of recovery from inactivation. However, it produced little change in the steady-state inactivation curve. The steady-state outward K^+ current (I_{SS}) was inhibited with an IC_{50} of $8.7 \mu M$. The inward rectifier K^+ current (I_{K1}) was also reduced by OMNC.

5 In the perfused heart model, OMNC (3 to $30 \mu M$) prolonged the ventricular repolarization time, the spontaneous cycle length and the atrial and ventricular refractory period. The conduction through the AV node and His-Purkinje system, as well as the AV nodal refractory period and Wenckebach cycle length were also prolonged ($30 \mu M$).

6 In conclusion, OMNC blocks Na^+ , I_{to} and I_{SS} channels and in similar concentrations partly blocks Ca^{2+} channels. These effects lead to a modification of the electromechanical function and may likely contribute to the termination of ventricular arrhythmias. These results provide an opportunity to develop an effective antiarrhythmic agent with modest positive inotropy as well as low proarrhythmic potential.

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Abbreviations: AERP, atrial effective refractory period; AH, atrio-His bundle conduction interval; APA, action potential amplitude; $APD_{50, 90}$, action potential duration measured at 50 and 90% repolarization; AVNERP, AV nodal effective refractory period; BCL, basic cycle length; G, conductance; HPFRP, His-Purkinje system functional refractory period; HV, His-ventricular conduction interval; I_{Ca} , Ca^{2+} inward current; I_{K1} , inward rectifier K^+ current; I_{Na} , Na^+ inward current; I_{SS} , steady-state outward K^+ current; I_{to} , transient outward K^+ current; k, slope factor; OMNC, *O*-methyl-neocaryachine; RMP, resting membrane potential; SA, sinoatrial conduction interval; τ , time constant; τ_f and τ_s , fast and slow time constant; VERP, ventricular effective refractory period; V_h , half-maximal potential; V_{max} , maximal upstroke velocity of action potential; VRT, ventricular repolarization time; WCL, Wenckebach cycle length