New Local Anesthetic Agents

To the Editor.—Recently, Wang et al.1 described the long-lasting local anesthetic effects of a lidocaine derivative, and stated that the search for long-acting local anesthetic agents with wide therapeutic safety margin has been ongoing for the past 2 decades. However, more than 40 years ago, researchers from Hungary reported on potent and long-lasting local anesthetics that belonged to higher alkyldialkyl quaternary derivatives of known local anesthetics.2–4

Previous developmental approaches for long-acting local anesthetics used various concepts, one of which used quaternary local anesthetics.5 With this class of agents, one important criterion is to obtain a suitable and stable protonated ammnonium (or other ionium) cation as the essential part of the local anesthetic molecule. Other criteria also must be met. For example, an adequate, yet variable, degree of lipophilicity versus hydrophilicity is required assured access to the fast ion channels and for suitable time pattern of action in different-sized nerve fiber populations that differ significantly in their thickness, composition, and physiologic properties. This also is required to satisfy criteria for different types of local or regional anesthesia. Therefore, regardless of the results obtained either in ion channel preparations, in isolated, desheathed, or intact nerve fibers, the most relevant test is to produce selective sensory block on in vivo models. Wang et al.1 performed both types of tests with two quaternary ammonium derivatives of lidocaine; one of which they call "tonicaine," suggesting that this agent is a new, clinically tested or at least therapeutically eligible new local anesthetic. Interested readers certainly would have liked to know how these two agents were selected. Was, for example, a broad structure-activity type of database available to the authors, or was the design of the agents largely based on computational modeling or other techniques that provided new insight? A further important point is that during "conventional" drug development processes, the question of local and systemic toxicity must be addressed in the earliest stages. Systemic toxicity with quaternary ammonium-type local anesthetics may include, in addition to or instead of the typical patterns of cardiac and CNS toxicity of tertiary amine type local anesthetics, effects on peripheral, particularly nicotinic, acetylcholine receptors. These may manifest in ganglionic or neuromuscular block. These factors may help determine the overall therapeutic safety margin of agents such as "tonicaine."

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References


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