CORRESPONDENCE

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In Reply.—We are grateful to Gyermek for his legitimate comments about the earlier development of quaternary derivatives as long-acting local anesthetics. We were aware of some of the work performed before 1970 as reviewed by Büchi and Perlía.1 These authors stated that procaine-ethylbromide and lidocaine-ethylbromide were less active than their parent compounds in vitro. They also commented about the work of Herr et al.2 on the methyl- and benzyl-halogenides of cocaine, tetracaine, and cinchocaine, which produced more vigorous activity, but suggested that “the above local anesthetics only slowly penetrate into and leave the membranes of the nerve pathways.” The slow action of these quaternary derivatives in vivo was stated clearly in one of the 1953 papers3; “in numerous cases it is 12–16 hr. before the effect develops.” Because of their slow onset of action, it is unclear whether the observed local anesthetic effects of such quaternary compounds are due to the nerve block, neurotoxicity, neuritis, and/or other unknown mechanisms. As for the potency of quaternary derivatives of benzoyl- and benzoyl-\(\psi\)- tropine, it was reported that “Thus the higher alkyl as well as aralkyl quaternaries show activities similar to those of tertiary compounds.”

The potency difference was minimal even for the most active derivative. The compound we synthesized, diethyl-(2,6-dimethylamidino-carbonyl)-methyl-\(\beta\)-phenylethyl ammonium bromide (named tonicaine for brevity), has a relatively fast onset time (<10 min) in blocking the sciatic nerve functions, suggesting that it can penetrate the membrane barrier more efficiently than other quaternary compounds. For future testing, we agree with Gyermek that the local and systemic toxicity studies should be performed before any large animal tests are initiated.

Finally, the design of our compound is based on three facts that were presented in the introduction of our article4: (1) the charged form of local anesthetics is the active form, (2) the permanently charged quaternary amiphatic compounds can be trapped easily within the cell after external drug application, and (3) the local anesthetic binding site consists mainly of two large hydrophobic binding domains. Obviously, these three facts alone will be of little use in drug design if the new compounds synthesized fail to penetrate the lipid bilayer efficiently. There are no sets of rules in our article for the design of a long-acting local anesthetic, as stated otherwise by Gyermek. What we did state was that “our results indicate that the receptor topology and the physico-chemical properties of the drug are both important in determining the local anesthetic potency in vivo.” Gyermek’s insight on the importance of the relative hydrophilicity and hydrophobicity of individual compounds is in agreement with our results, and remains one of the most relevant factors in the design of therapeutical local anesthetics.

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