Local Anesthetics: Inhibition of Subcutaneous Absorption in Rats[1] (34647)

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When local anesthetics are injected into highly vascular areas the agent may be absorbed into the circulatory system so rapidly that a means of decreasing blood flow must be used to allow more time for interaction between drug and nerve fibers. Thus, Von Braun (1) found that adequate local anesthesia would not be produced by procaine unless it was used in combination with a vasoconstrictor, such as epinephrine. Local anesthetics, except cocaine, have been shown to possess vasodilator action (2) which contributes to rapid circulatory absorption thereby increasing the need for added vasoconstrictor.

Recently, newer local anesthetics (such as lidocaine, mepivacaine, and prilocaine) have been used effectively in clinical practice with less (or even without) vasoconstrictors (3–5). It was difficult for us to understand why there should be such a difference in requirement for vasoconstrictor among local anesthetics in view of their similar vasodilator properties when injected intra-arterially (6, 7). We reasoned that this difference could be based on a differential effect of the local anesthetics upon the microcirculation.

In an earlier study (8), four local anesthetics (procaine, mepivacaine, lidocaine, and prilocaine) were reported to decrease ^{32}P-Phosphate (^{32}P) clearances from rat subcutaneous tissue. The present studies were designed (i) to include local anesthetics of different chemical classes and potencies, (ii) to quantify the relationship between concentration of local anesthetic and effect upon clearance, and (iii) to ascertain whether the clearance inhibition found in the previous study was related to the isotopic substance used.

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Methods. The isotope clearance method of Kety (9) was used to determine "capillary efficiency." Iodoantipyrine (IAP) was labeled according to a method involving an exchange reaction between $^{131}I^-$ and 4-iodo-antipyrine (10). The final product never contained more than 1.5% iodide contamination under the conditions of our experiments. Control clearances were measured by external monitoring of the disappearance of the IAP given in a saline–phosphate buffer (pH 7.5) using a Nuclear Chicago surgical scintillation probe (model 931) connected to an appropriate recording apparatus. The control solution (0.05 ml) was injected subcutaneously in the dorsal lumbosacral midline of 150–250 g rats which were anesthetized with sodium pentobarbital (40 mg/kg).

Experimental clearances were determined at similar nearby sites after injecting solutions containing both the buffered isotope and local anesthetic. Hydrochloride salts of cocaine, procaine, lidocaine, prilocaine, and tetracaine were studied at concentrations of 0.1, 0.5, 1.0, and 5.0%. Only three clearance measurements (one control and two experimentals) were obtained in one rat. The order of control and experimental injections was varied in different rats.

Results are expressed as the initial clearance rate (C_i) defined as the slope of the early (2.5–7.5 min) straight-line portion of a plot of remaining radioactivity vs. time (Fig. 1). C_i is used as an approximation of the k value of the function derived by Kety (9), $A_t = A_0 e^{-kt}$, where A_t and A_0 equal amount of radioactivity at time t and 0, respectively. Either C_i or k can be used as a relative indicator of capillary efficiency, but the former saves the necessity of extrapolation to 0 time and of graphic analysis.

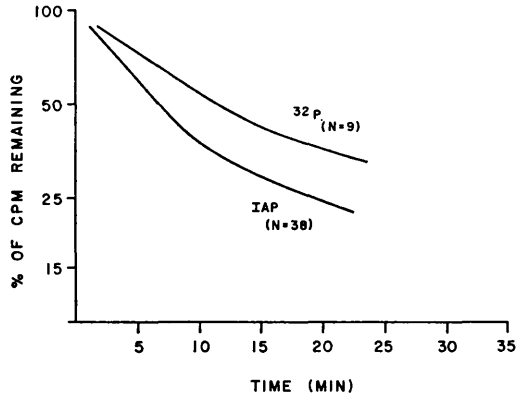

FIG. 1. Clearances of ^{32}P-PO$_4$ and ^{131}I-IAP from rat subcutaneous tissue.

Results. In Fig. 1, average ^{32}P and IAP clearances are shown. The C_l of IAP was greater than that of ^{32}P (8.2 ± 0.37 vs. 4.3 ± 0.75). Control clearances were reproducible when data from several rats were compared or for three clearances in the same rat. Figure 2 is a plot of C_l for IAP vs. concentration of local anesthetic. The only increase of clearance found was for tetracaine at 0.1%. Tetracaine (0.5%) and procaine (0.1 or 0.5%) showed no significant difference from control clearance rates. Higher concentrations of tetracaine and procaine inhibited IAP clearance. Lidocaine, prilocaine, and cocaine were inhibitors at all concentrations. The order of potency was cocaine > prilocaine > lidocaine > procaine > tetracain. (When Fig. 2 was replotted in terms of molar concentrations, the relative positions of the local anesthetic lines remained unaltered. However, cocaine's line was shifted to the left, indicating a slightly greater potency than depicted.)

The inhibition of clearance caused by local anesthetics was unexpected because of their reported vasodilating effects. All of the other vasodilators (aminophylline, papaverine, cholinergics, etc.) in our system increased clearance, as reported previously (8, 11).

Discussion. Effects of local anesthetics on IAP clearances are consistent with results reported earlier using ^{32}P (8) where relative inhibitory potencies were prilocaine > mepivacaine = lidocaine > procaine. The order of potency for clearance inhibition is not related to relative nerve blocking potencies. Clearance inhibition appears to be inversely related to the clinical need for added vasoconstrictor, *i.e.*, procaine > lidocaine > prilocaine > cocaine. [Tetracaine even without vasoconstrictor is long acting, a property which is apparently related to its lipophilic nature (15)].

Although arteriolar dilation (6, 7) has been observed due to systemic administration of local anesthetics the results of topical application upon vascular beds is more variable. For example, Holler (12) reported that lidocaine caused vasoconstriction in the web of frog foot, but vasodilation when applied to the mesentery of cats. Procaine caused vasodilation in both vascular beds. Pohto and Shienen (13) found that mepivacaine or lido-

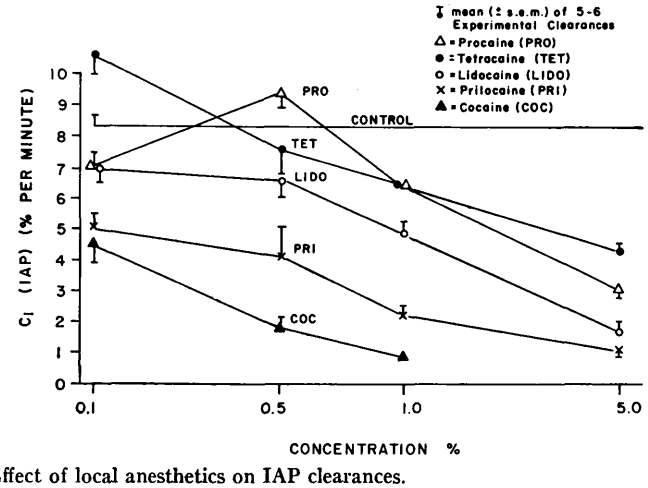

FIG. 2. Effect of local anesthetics on IAP clearances.

caine retarded blood flow when applied to the dental pulp through a thin layer of dentine.

To explain why local anesthetics cause inhibition of isotope clearance in rat subcutaneous tissue, the autoinhibitory hypothesis of Schou (14) may be used. Locally injected drugs may inhibit absorption (autoinhibition) by the release of potent vasoactive local hormones. Luduena (15) recently reviewed evidence that local anesthetics cause autoinhibition. This mechanism appears to be dependent upon species as well as the spectrum and quantities of local hormones present in various tissues. The rat shows the greatest autoinhibiton, possibly because of mast cell serotonin stores (14). The net microcirculatory effect of a local anesthetic appears to be a balance between autoinhibitory effects and direct smooth muscle action.

Summary. Local anesthetics inhibited the clearance of 4-iodoantipyrine when injected into rat subcutaneous tissue. The order of potency for the inhibition was cocaine > prilocaine > lidocaine > procaine >tetracaine. This order is not the same as their local anesthetic potencies. The inhibition of clearance suggests that the local anesthetics have an effect on capillary uptake in the rat which is not related to their well-known vasodilator effect.

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