11596

Effect of Atropine on the Local Action of Procaine.

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Since the discovery of local anesthetics attempts have been made to obtain a prolongation of their action.

Modification of physical properties, such as tonicity and neutrality, forming of various salts, as well as increasing concentration does not lead to any satisfactory prolongation.[1, 2] Epinephrine has been recommended and is widely used; however it is generally recognized that this drug has a large range of contra-indications: in vasolabile patients, in patients with Graves' disease, and in surgery of very vascular areas (teeth, tonsils) with the dangers of quick resorption or accidental intravenous injection. It has also been shown that the addition of epinephrine to procaine injected intra-

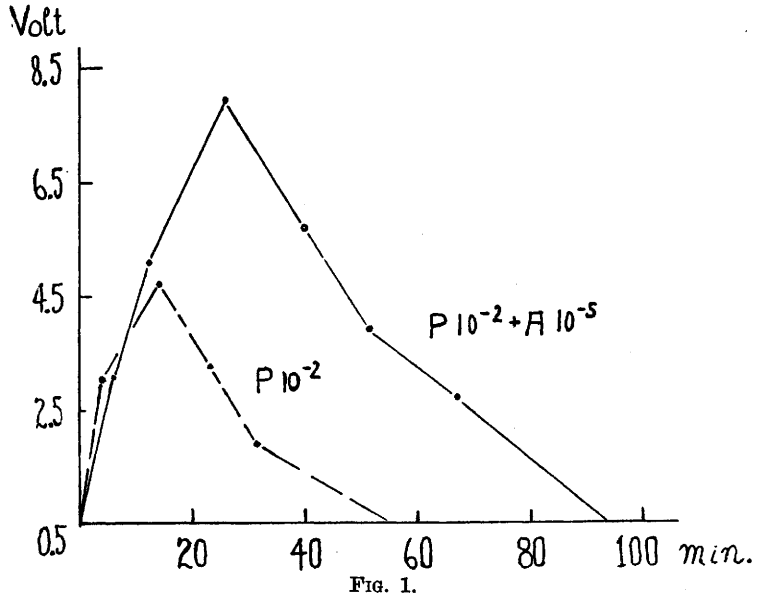

Fig. 1.

Anesthesia of the rabbit's cornea produced by Procaine HCl 1:100 without (P 10–2) and with Atropine sulfate 1:100,000 (P 10–2 + A 10–5).

Abscissa: Duration of anesthesia in minutes.

Ordinate: Least amount of electric stimulus in volts (from the secondary coil of the inductorium) producing wink reflex.

[1] Hirschfelder, A. D., and Bieter, R. N., *Physiol. Rev.*, 1932, **12**, 190.

[2] Leser, A. J., *J. Pharm. and Exp. Ther.*, 1940, **68**, 389.

venously into the guinea pig increases the toxicity of procaine 30-40 times.[3]

In an effort to replace epinephrine, addition of different drugs to procaine had been tried previously.[4] As it seemed possible that a parasympathetic depressant would exhibit an effect similar to that of a sympathetic stimulant (epinephrine) atropine was used in the further course of these experiments. The drug was added to a 1% solution of procaine HCl, which was then injected under the conjunctiva of a rabbit's eye. Corneal sensitivity was determined by means of an inductorium; the details of the test are described elsewhere.[2]

The graph shows the effect of atropine on procaine anesthesia. A slight increase in intensity and a very remarkable prolongation of anesthesia was obtained with concentrations of atropine sulfate as low as 10^{-5} (48 experiments). With these small amounts of atropine a diffuse bleaching of the conjunctiva was noted; dilatation of the pupil did not exceed the degree occasionally observed with procaine alone. Addition of atropine in higher concentrations 10^{-3} (12 experiments) resulted in a marked reddening of the conjunctiva and dilatation of the pupil, and showed no definite effect on intensity or duration of procaine anesthesia. It is possible that some systemic or vagal effects obtained with these higher concentrations interfere with the purely local action of atropine in low amounts.

The anesthetic action of atropine 10^{-5} has been found equal to about 10^{-3} of procaine HCl. This slight anesthetic effect is well known (Sollmann[5]) and may be correlated with the chemical relationship of atropine and cocaine as tropine derivatives. On the basis of pure summation the addition of atropine sulfate 10^{-5} to procaine HCl 10^{-2} would equal an increase of procaine concentration by 0.1%, which is known to give only very little prolongation.[6]

The effect of atropine sulfate 10^{-3} and 10^{-5} on the permeability of the frog's skin was tried. Small areas of skin of pithed frogs were cut out and left for 10-30 minutes in solutions of atropine 10^{-3} and 10^{-5} in frog-Ringer; controls from symmetrical areas were left in normal frog-Ringer. The membranes were mounted on small glass tubes with their surface outside. The tubes were immersed into a N/10 sodium thiocyanate solution and filled with ferric chloride in frog's Ringer as indicator. Temperature (20°C) and the amount of fluid used were kept constant. The degree of diffusion of thiocyanate

3 Eichholtz, F., and Hoppe, G., *Arch. f. exp. Path. u. Pharm.*, 1933, **173**, 687.

4 Leser, A. J., and Scholl, R., *Wien. klin. Wschr.*, 1937, **50**, 1577.

5 Sollmann, T., *Manual of Pharmacology*, 5th ed., W. B. Saunders, 1936.

6 Sinha, H. K., *J. Pharm. and Exp. Therap.*, 1936, **57**, 199.

ions through the membrane is indicated by the intensity of the color (red) in the tubes Although frog skins show a wide range of individual variation a careful comparison of symmetrical skin-areas seemed justified. Atropine 10^{-5} resulted in a decrease of permeability of the membrane for thiocyanate as indicated by the color test, while higher concentrations (10^{-3}) showed no definite effect. The same was true of the stain taken up by the membranes after 24 hours. These results suggest that prolongation of procaine anesthesia by atropine may be due to changes in permeability.

Results obtained with other drugs of the atropine group, acetylcholine, as well as clinical trials will be reported elsewhere; it may be stated here that syntropan seems to be superior to atropine.

Summary. Prolongation of procaine HCl anesthesia by addition of atropine sulfate in low concentration 10^{-5} is reported; tests were made on rabbit's cornea after subconjunctival injection. The possibilities of an effect of low amounts of atropine sulfate on permeability are discussed.

Acknowledgment is due to Prof. A. J. Clark (University of Edinburgh) for suggestions and interest in the first stage of these experiments and to the Earl Moray Fund of the University of Edinburgh for financial aid.

11597

Sulfanilamide, Sulfapyridine and Sulfathiazole and Experimental Infections in Mice Due to *Shigella paradysenteriae* Flexner.

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Our earlier studies[1] of acute diarrhea in 207 infants and young children revealed that 50% of the patients who were admitted to the Children's Hospital during the summer of 1938 with diarrhea had dysentery bacilli *(Shigella paradysenteriae)* in their stools. The majority of these patients were infected with the Flexner type, a few with the Sonne type. The mortality was 17%. With the advent of sulfanilamide and allied compounds and a search of the

[1] Cooper, M. L., Furcolow, M. L., Mitchell, A. G., and Cullen, G. E., *J. Pediat.*, 1939, **15**, 172.