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Adsorbents for Procaine-Epinephrine Solutions.

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Mixtures of procaine and epinephrine have long been employed as local anesthetics. Epinephrine, by causing local vasoconstriction, holds the procaine near the injected area, localizing and prolonging the anesthesia. There is risk, however, of the epinephrine entering the general circulation, especially when the anesthetic is injected into the vascular tissue of the gums and palate in dental surgery. The undesirable effects of epinephrine in dental anesthetics have been emphasized by Miller,[1] Stuart,[2] and Tainter, Throndson and Moose,[3-5] whose clinical studies show various degrees of rise in blood pressure, increase in heart rate, extrasystoles and increase in respiratory rate following the submucosal injection of procaine-epinephrine solutions. Pickering, McCooey, Steinmeyer and Luckhardt[6] injected procaine-epinephrine solutions in dogs in sites commonly used in dental operations and obtained marked rises in blood pressure.

Methods. The purpose of the present experiments is to find a substance which will retard and diminish the undesirable pressor action of epinephrine and procaine in the main circulatory system, while still allowing it to prolong the anesthesia by local vasoconstriction. An adsorbent for epinephrine which will produce such a retarding effect is now being sought. It would also be desirable for procaine to be adsorbed and to be given off slowly as needed to maintain anesthesia. Colloidal tri-calcium phosphate, used extensively as an adsorbent for proteins, was the first substance tested.

Dogs anesthetized with paraldehyde were used in these experiments. Both vagi were sectioned to prevent reflex slowing of the heart by the carotid sinus and aortic arch mechanisms. Blood pressure and respiratory rate and amplitude were recorded on kymo-

1 Miller, H. C., *J. Am. Dental Assn.*, 1937, **24**, 515.

2 Miller, J. C., and Stuart, C. W., *J. A. D. A.*, 1936, **23**, 1883.

3 Tainter, M. L., Throndson, A. H., and Moose, S. M., *J. A. D. A.*, 1937, **24**, 376.

4 Tainter, M. L., Throndson, A. H., and Moose, S. M., *J. A. D. A.*, 1938, **25**, 1321.

5 Tainter, M. L., and Throndson, A. H., *J. A. D. A.*, 1938, **25**, 966.

6 Pickering, P. P., McCooey, C. J., Steinmeyer, H. P., and Luckhardt, A. B., *J. A. D. A.*, 1939, **26**, 1823.

graph paper in the usual manner. As a control, 2 cc of 2% procaine containing 1:25,000 epinephrine was injected directly into the anterior palatine, mental and posterior palatine foramina. The plunger of the syringe was always retracted prior to the injection to exclude the possibility of direct entrance of the solution into a vein. The time of injection was kept as constant as possible and averaged about 20 seconds.

To test the effect of the colloidal $Ca_3(PO_4)_2$ on epinephrine, 2 cc of $Ca_3(PO_4)_2$ containing 1:25,000 epinephrine was injected into the foramina on the side opposite those employed in the control part of the experiment, using the same dogs. The effect of intravenous injection of $Ca_3(PO_4)_2$ with 1:25,000 epinephrine was compared with intravenously injected 2% procaine with 1:25,000 epinephrine. Chemical tests for adsorption were also made. The supernatant fluid from centrifuged $Ca_3(PO_4)_2$-epinephrine mixtures was analyzed for epinephrine colorimetrically, using Barker, Eastland and Evers' modification of the Ewin test.[7]

To test the ability of $Ca_3(PO_4)_2$ to adsorb and thus retard the action of procaine, comparisons are planned of the duration of anesthesia produced by plain procaine with that produced by $Ca_3(PO_4)_2$-procaine mixtures. Preliminary tests are being made on the pressor effect of submucosal injection of epinephrine in peanut oil, which was first introduced by Keeney[8] for the alleviation of asthma.

Results. The present experiments, in which 19 dogs were used, confirm the findings of Pickering, *et al.,* with respect to the increase in blood pressure following the submucosal injection of procaine-epinephrine mixtures. The accompanying table shows that the pressor effect of epinephrine injected submucosally is greatly reduced by the addition of colloidal $Ca_3(PO_4)_2$. In all 3 sites the average percentage increase in blood pressure following the injection of procaine-epinephrine mixtures was greater than that after the injection of epinephrine treated with $Ca_3(PO_4)_2$. The differences in the two means for each site were found to be statistically significant when analyzed by methods described by Fisher.[9]

$Ca_3(PO_4)_2$ with 1:25,000 epinephrine when administered intravenously in dogs gave nearly as great a pressor effect as 2% procaine with 1:25,000 epinephrine. The colorimetric tests on the supernatant liquid from centrifuged colloidal $Ca_3(PO_4)_2$-epineph-

[7] Barker, J. H., Eastland, C. J., and Evers, N., *Biochem. J.*, 1934, **26**, 2129.

[8] Keeney, E. L., *Am. J. Med. Sci.*, 1939, **198**, 815.

[9] Fisher, *Statistical Methods for Research Workers.*

TABLE I.
Average Percentage Increase in Blood Pressure Following Submucosal Injections.

Solution	Vol. of injections	No. of animals	Avg % increase in blood pressure		
			Ant. palatine	Mental	Post. palatine
Procaine 2% with epinephrine 1:25,000	2.0 cc	19	43.1	21.9	11.6
$Ca_3(PO_4)_2$ epinephrine 1:25,000	2.0 "	19	11.5	11.4	4.0

rine mixtures showed that the supernatant fluid contained epinephrine at as great a concentration as did the original solution.

Conclusions. It is quite apparent that colloidal $Ca_3(PO_4)_2$ diminishes the pressor effect of submucosally injected epinephrine.

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Survival of the Respiratory (Gasping) Mechanism in Young Animals Subjected to Anoxia.

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Various observers (Reiss and Haurowitz,[1] Avery and Johlin,[2] Kabat and Dennis,[3] Selle and Witten,[4] and Himwich, Alexander and Fazekas[5]) have reported that young animals are much less susceptible to anoxia and asphyxia than adults. The present studies were undertaken to determine whether the primitive respiratory mechanism (gasping) itself survives longer in the young than in the old.

Movements of the mandible of various species (dogs, cats, rabbits, and rats) were recorded mechanically following complete and rapidly induced anoxia produced by ligation of the cerebral vessels or by decapitation. In preliminary experiments it was

1 Reiss, M., and Haurowitz, F., *Klin. Wchnschr.*, 1929, **8**, 743.

2 Avery, R. C., and Johlin, J. M., PROC. SOC. EXP. BIOL. AND MED., 1932, **29**, 1184.

3 Kabat, H., and Dennis, C., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 534.

4 Selle, W. A., and Witten, T. A., *Proc. Am. Physiol. Soc.*, 1941, **53**, 253.

5 Himwich, H. E., Alexander, F. A. D., and Fazekas, J. F., *Proc. Am. Physiol. Soc.*, 1941, **53**, 193.