

A COMPARISON OF THE IRRITANT ACTION OF CONESSINE, ISOCONESSINE, AND NEOCONESSINE

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Conessine is a powerful local anaesthetic, but its use is limited since its injection produces inflammation which may be followed by necrosis. Isoconessine and neoconessine are isomers of conessine and they also possess local anaesthetic actions. It was therefore of interest to compare their irritant action with that of conessine.

No method for comparing the irritant action of different substances in animals has hitherto been described and a method has been used which is in some respects similar to the guinea-pig skin test for diphtheria antitoxin and for old tuberculin. In a preliminary experiment 0.2 ml. of 1 in 50, 1 in 100, 1 in 200, 1 in 400, and 1 in 800 solutions of conessine dihydrochloride were injected intracutaneously into a guinea-pig and the weals produced by the injection were ringed with ink. During the next three days no effect was apparent at the site of injection of the 1 in 800 solution, while the 1 in 400 solution produced only a very slight inflammation. The higher concentrations produced progressively greater effects and at 72 hours the site of the injection of the 1 in 50 solution was covered by scar tissue. The fact that these concentrations produced an appreciable and graded response indicated that a comparison could be made in this way.

In order to compare the effects produced by the different substances, guinea-pigs were prepared by removing the hair from the back with electric clippers. The back was marked out into 6 areas, 3 on each side of the spine, and 0.2 ml. of each of 3 concentrations of one alkaloid (1 in 50, 1 in 100, and 1 in 200) were injected on one side and the same concentrations of a different alkaloid on the other side. In half the animals the solutions were injected in increasing strength towards the head and in the other half this order was reversed. Each concentration of each alkaloid was injected into 6 animals. Inflammation appeared within about 2 hours and a first attempt to compare the effects was made between 2-4½ hours after the injection.

Scores from 0 to 3 were awarded according to the amount of inflammation. After 24 hours the inflammation was more marked and scar tissue was beginning to appear. Estimates of the effects were again made, the range of scores being increased in accordance with the increased effect. After 72 hours the inflammation had largely disappeared and was replaced by scar. Scores from 0 to 6 were again given to the different areas. Two other observers also examined the areas and allotted scores to each. Their results were similar to those already obtained.

The mean result for each concentration of each alkaloid was plotted as an ordinate against the concentration as abscissa (using a logarithmic scale) in Fig. 1, in which the relation between the alkaloids

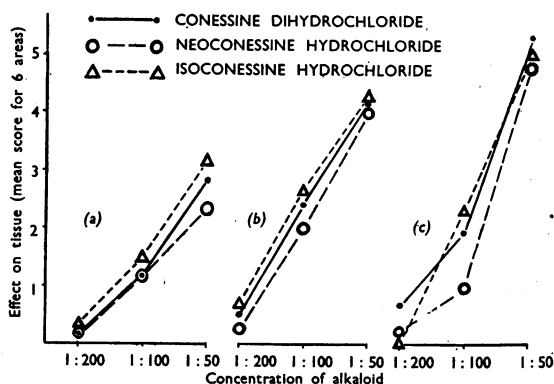


FIG. 1.—Graphs showing the estimates made by one person of the amount of inflammation and necrosis after the injection of varying concentrations of conessine and its isomers. (a) 2-4½ hours after injection; (b) 24 hours; (c) 72 hours.

is shown as estimated at (a) 2-4½ hours, (b) 24 hours, and (c) 72 hours after injection. Fig. 1 shows that neoconessine causes slightly less inflammatory reaction than the others, but the difference is very small. All three substances begin to pro-

duce inflammation in a concentration of 1 in 200. The smallest concentration producing local anaesthetic action is in the range 1 in 6,400 to 1 in 3,200 (Stephenson, 1948); this, however, is a very slight degree of anaesthesia. More is obtained in the range 1 in 1,600 to 1 in 800, which is still well below the concentration causing inflammation.

Solutions containing adrenaline.—Procaine is commonly mixed with adrenaline, and its local anaesthetic action is greatly increased thereby. It seemed possible that the local anaesthetic action of conessine might also be increased if adrenaline were mixed with it, and a comparison was therefore carried out in which solutions of conessine were compared with similar solutions containing adrenaline. Six guinea-pigs were used, and the results obtained by the method of Bülbring and Wajda (1945) are shown in Table I.

TABLE I

0.2 ml. solution is injected intradermally. The area is pricked 6 times at 5, 10, 15, 20, 25, and 30 min. after injection. The number of times there is failure to respond is observed and is shown below. The maximum number of failures is 36

Pig No.	Conessine			Conessine + Adr. 1 in 100,000		
	1 in 830	1 in 1660	1 in 3320	1 in 830	1 in 1660	1 in 3320
1	36	25	15	35	34	30
2	21	20	10	29	27	20
3	29	26	27	33	20	12
4	35	22	15	35	28	15
5	35	26	26	36	28	21
6	29	20	0	35	32	25
Mean	31	23.1	15.5	33.8	28.1	20.4

Table I shows that the presence of adrenaline caused some increase in the duration of anaesthesia produced by conessine, but less than that with procaine. The difference can be expressed by saying that the addition of adrenaline would enable a solution containing 1 in 1,000 conessine dihydro-

chloride to act like a solution containing 1 in 700.

In view of the fact that the work of R. D. Haworth and Nazar Singh (1948) indicates that conessine is a steroid, it may well be that it is less readily absorbed from the site of injection than procaine. Thus the fact that adrenaline does not so greatly intensify its local anaesthetic action within the period of 30 min. observation is not surprising.

Experiments were also made to observe whether the addition of adrenaline to a solution of conessine would alter the irritant action of the solution. Solutions of conessine dihydrochloride containing adrenaline 1 in 100,000 were compared with the same solution, without adrenaline. The conessine solutions were 1 in 400, 1 in 200, and 1 in 100; each solution was injected on one side of the back of a guinea-pig and compared with the same solution containing adrenaline on the other side. Two animals were used, and in neither was any difference observed owing to the presence of adrenaline. The 1 in 100 solution produced obvious inflammation, followed by necrosis. The 1 in 200 solution produced less inflammation and an induration at the site of injection.

SUMMARY

A method of making a quantitative comparison of two or more substances for local irritant action is described. Conessine, isoconessine and neoconessine all begin to cause inflammation after intracutaneous injection in a concentration of 1 in 200. The local anaesthetic action of conessine is intensified when adrenaline (1 in 100,000) is present by about 40 per cent. The presence of adrenaline does not affect the irritant action of conessine.

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