THE "SPECIFIC" ANALGESIC EFFECT OF TRICHLORETHYLENE UPON THE TRIGEMINAL NERVE

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DISCUSSING intoxication with industrial trichlorethylene, Plessner [1] and Oppenheim [2] pointed out frequent trigeminal anesthesias. They later claimed remarkable results in the treatment of "tic douloureux" with inhalations of TCE and suggested a specific analgesic effect of the drug on the fifth cranial nerve. Their findings were not confirmed by Glaser,[3] Geiger,[4] and Rubinstein [5] and were challenged by Gerbis,[6] Kalinowski,[7] and later by Krantz.[8] Nevertheless, the theory of a specific action on the trigeminal nerve has prevailed, as evidenced by the use of trichlorethylene in the treatment of tic douloureux and statements found in several textbooks of pharmacology and anesthesia.

Little experimental work has been done to verify that theory; only two publications related to that problem have been published. Rubinstein [9] showed that in dogs anesthetized with ether or trichlorethylene, faradic stimulation of the dura (trigeminal innervation) or of the sciatic nerve did not produce the variations in blood pressure seen in alert animals. During awakening with both agents, as soon as the sciatic reflex on the blood pressure returned, a similar response was obtained from dural stimulation. The author concluded that trichlorethylene had no specific action upon the trigeminal nerve.

Hardy, Wolff and Goodel [10] measured the pain threshold of the forehead and the back of the hand in three human subjects, after inhalation of 1 ml. of trichlorethylene. In both areas, the pain threshold was increased by nearly 45 per cent after 15 minutes, but the effects lasted two hours for the forehead as opposed to 40 minutes for the back of the hand. This would suggest a more efficient analgesia of the trigeminal territory.

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METHOD

The effects of trichlorethylene upon the trigeminal and spinal nerves of rabbits have been compared simultaneously. Two methods used frequently in experimental analgesimetry have been selected:

(1) *For the trigeminal nerve:* the tooth pulp method, as modified by Yim *et al.*[11] Insulated metal electrodes were attached to holes previously drilled in the rabbits' upper incisors. Square wave monophasic pulses of 0.1 millisecond at a frequency of 25 per second were delivered from a Grass stimulator S4-A in bursts of stimuli of one second duration. Supra-threshold stimuli were given and the voltage gradually decreased until chewing was not observed, and the lowest voltage producing a response recorded as the threshold. Intervals of at least 30 seconds were maintained between determinations. The increase in pain threshold was expressed in per cent increase over the preanalgesic level.

(2) *For the spinal nerve:* the skin twitch reflex to radiant heat. A slight modification of a technique proposed by Ercoli and Lewis [12] was used. Two-inch diameter spots were painted with India ink on the shaved back of the animal, close to the spine. We attached in front of a commercial model of a Hardy-Wolff-Goodel algesimeter, a lens designed to focus the light provided by a 500 watt projection lamp at a point 8 inches from the diaphragm. The intensity was maintained at 450 milliamperes, the time of application being the variable. A minimal interval of 60 seconds was kept between measurements. The minimal period of latency to produce a skin twitch was called the threshold and the effect of the analgesic expressed as above in percentage increase of the initial threshold.

We measured the depression of a reflex and not a phenomenon as complex as pain relief. However, the expression "pain threshold" has

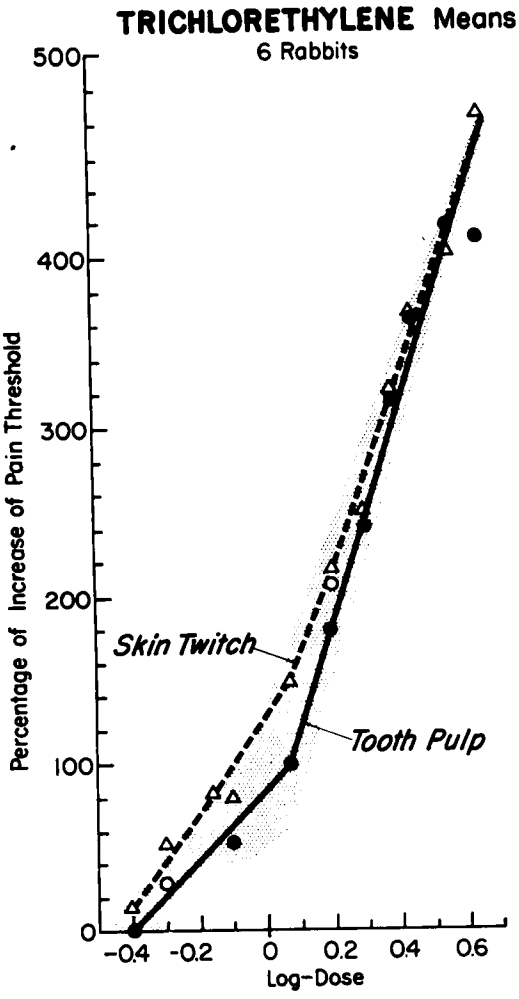

FIG. 1. Experiment 1. Increase of pain threshold plotted against concentrations of trichlorethylene (means of 6 rabbits).

generally been accepted in experimental algesimetry and will therefore be used here to simplify further description.

As suggested by Miller,[13] intensity and duration are two factors which might have to be considered when estimating the potency of an analgesic; in view of that fact and of the findings of Hardy and associates,[10] not only absolute values of thresholds (first experiments) but also duration of analgesia (second experiment) were compared in the present study.

Preliminary investigations suggested that the rabbits responded in a coherent way to both techniques. We were unable to detect differences of threshold between races and colors, but as already pointed out by Winder *et al.*,[14] we noticed that young animals (600–900 Gm.) responded more predictably and were therefore utilized. Each animal was used only once. Their teeth were drilled and their backs shaved 24 to 36 hours prior to the experiments, after intravenous injection of 25 mg./kg. pentobarbital. As much as possible, experimental conditions were maintained constant, especially those factors susceptible to modify the pain threshold as specified by Beecher [15] (minimal light, constant temperature of 70 F., absence of noise, isolation from other animals). Our preliminary experiments suggested that the rabbits would respond more predictably if several stimuli were applied before a response was studied in a new animal (we used a different area in the case

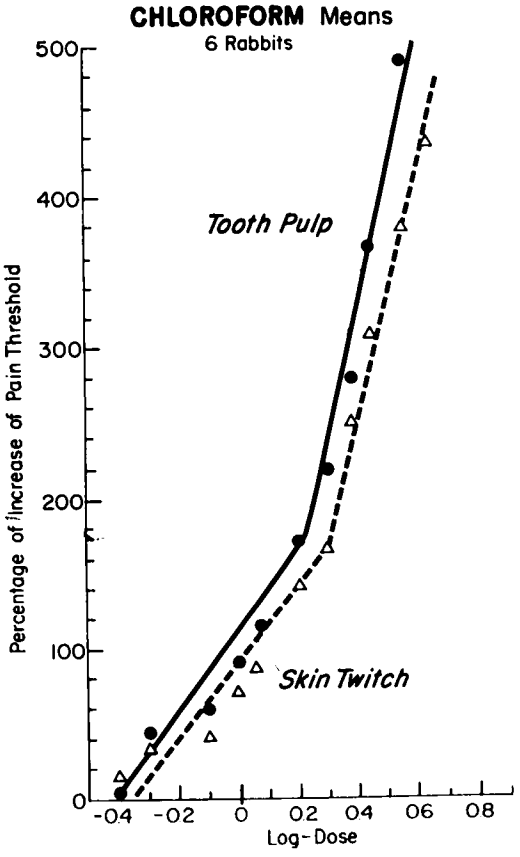

FIG. 2. Experiment 1. Increase in pain threshold plotted against concentrations of chloroform (means of 6 rabbits).

of radiant heat to avoid excessive damage to the skin).

First Experiment. Six young rabbits were utilized for each agent. Trichlorethylene and chloroform were administered through a F.N.S. vaporizer (maintained at "full" level) connected on one side to an anesthesia machine delivering two liters per minute of oxygen and on the other side to a plastic nonrebreathing mask covered with a rubber diaphragm through which the nose of the animal was inserted.[16]

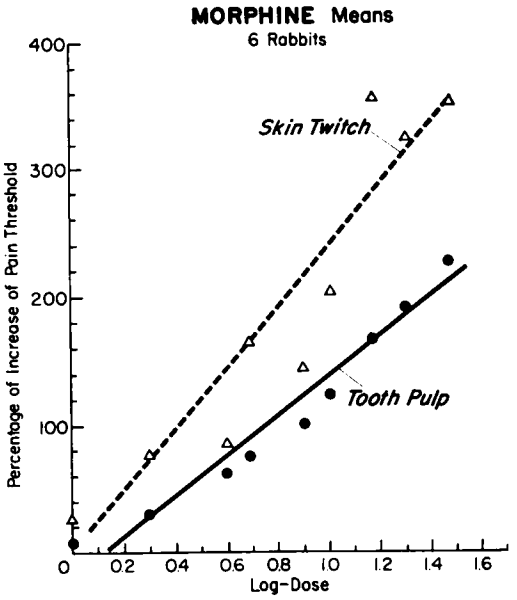

FIG. 3. Experiment 1. Increase in pain threshold plotted against doses of morphine (means of 6 rabbits).

The concentrations recorded indicate the settings of the vaporizer and no pretense is made to have determined the concentrations actually administered to the rabbits.

Each animal was first given oxygen for ten minutes and an initial threshold recorded, then varying concentrations, in increasing order, were administered for 10 minutes and the new threshold determined. Morphine was given subcutaneously in doses of 1-2-4-8-10-16-20-32 mg./kg. to six different rabbits for each dose and its analgesic effect checked one hour after injection. Doses and concentrations were converted to log-doses.

Second Experiment. Twelve animals were used for trichlorethylene, and six for chloroform and for morphine. All three drugs were administered subcutaneously: trichlorethylene and chloroform in 0.5 ml./kg. and morphine in 10 mg./kg. doses. The pain threshold was determined after 5 and 15 minutes, then every 15 minutes until it was back to its preinjection values. For the skin twitch reflex, five spots were tested before the analgesic was administered. Then for each following determination, a different spot was used, *e.g.*, after 5 minutes spot 1, after 15 minutes spot 2, 30 minutes spot 3, etc. Damage to the skin was thus minimized.

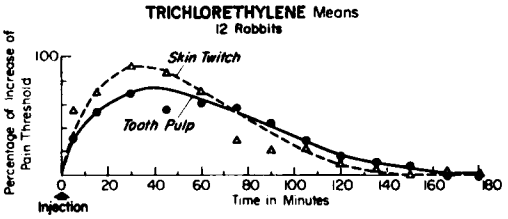

FIG. 4. Experiment 2. Increase in pain threshold plotted against time following injection of trichlorethylene (means of 12 rabbits).

RESULTS

First Experiment. Figure 1 shows the mean increase in pain threshold of the 6 rabbits inhaling the trichlorethylene, for both tooth pulp and skin twitch methods. The means have been plotted against the log-doses and the estimated regression lines drawn. Figures 2 and 3 represent the same findings for chloroform and morphine respectively.

Second Experiment. Figure 4 records the mean threshold increases of 12 rabbits obtained with each method at variable intervals

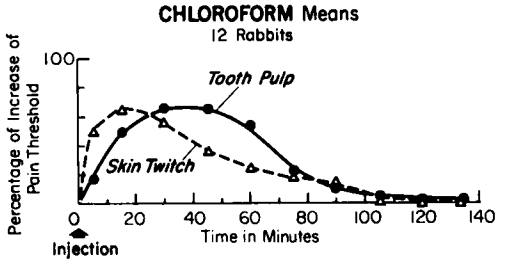

FIG. 5. Experiment 2. Increase in pain threshold plotted against time following injection of chloroform (means of 12 rabbits).

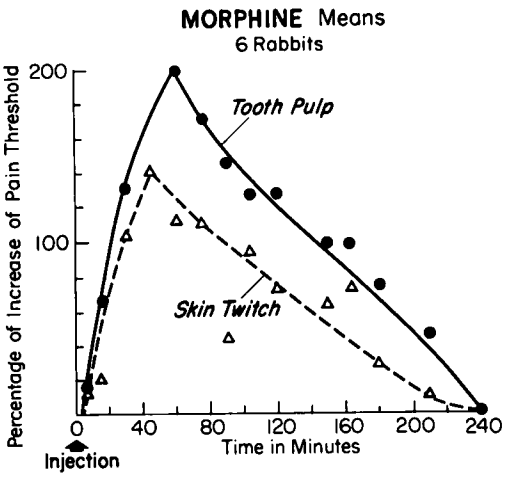

FIG. 6. Experiment 2. Increase in pain threshold plotted against time following injection of morphine (means of 6 rabbits).

after administration of trichlorethylene. Figures 5 and 6 represent the same findings for chloroform and morphine respectively.

STATISTICAL COMPUTATIONS

The terminology and notation of Dixon and Massey [17] were adopted for our computations.

Experiment 1 with Trichlorethylene (Fig. 1). We assumed that the two segments of the regression curve (thresholds against log-doses) in the tooth pulp method were linear. An analysis of variance showed $F = 0.48$ and $F = 0.62$ for the first and the second portions of the curve respectively. Since $F95$ was $F95(1.24) = 0.42$ and $F95(5.35) = 2.5$ respectively, F in both cases was not significant and our hypothesis of a linear regression was therefore correct.

We arrived at the same conclusions for the skin twitch method.

The estimated regression equations were then calculated and graphically represented. Thus we found for the tooth pulp:

(1) First part of the slope:

$$Yx = 46.02 + 189.69(X + 0.18)$$
$$sxy = 15.95 \text{ (assumed to be constant for all the log-doses)}$$

(2) Second part of the slope:

$$Yx = 326.66 + 528.07(X - 0.41)$$
$$sxy = 53.04 \text{ (also assumed to be constant for all the log-doses)}$$

Assuming that the distribution of the thresholds for any given log-dose was a normal distribution, we then determined the 95 per cent confidence limits for μy. Thus for instance in part 1: $\mu y - 0.3 = 22.9 \pm 21.47$. In part 2:

$$\mu y \ 0.2 = 204.26 \pm 32.07$$
$$\mu y \ 0.44 = 342.5 \pm 18.32$$

The limit values of μy were represented on figure 1 by a shaded area. The mean values of the skin twitch method are almost all included in the shaded area. This would suggest that at the 0.05 level, there is no significant difference between the values of pain threshold obtained in the trigeminal and spinal territories.

Similar calculations were effected for chloroform and gave similar results. The results of morphine revealed a significant difference, as their graphic representation seemed to indicate.

Experiment 2 with Trichlorethylene (Fig. 4). The differences of duration of analgesia between the two nerves were studied (1) when the threshold was down to 50 per cent of its maximum value, and (2) when it was back to its preinjection level. A Student's t test was applied to determine whether variations in duration were significant.

Thus for trichlorethylene at 50 per cent of maximum threshold value, "t" was found to be 1.5 for $n = 11$ would correspond to P between 0.1 and 0.2.

At the preinjection threshold value, "t" was found to be 1.2 which for $n = 11$ would correspond to $P \simeq 0.25$.

For both values, therefore, the differences were not statistically significant at the 0.05 level. A similar computation for chloroform and morphine revealed no significant differences at the same 0.05 level.

Our results, their graphic representation, and their statistical computation suggest that little—if any—difference exists between the effects of trichlorethylene upon the two reflexes either in time or intensity. Chloroform appears to act in a very similar manner. Our findings would indicate that morphine is more effective on the skin twitch than on the tooth pulp chewing reflex, at least as far as intensity is concerned. This contradicts the classical opinion of the excitatory effects of morphine on the spinal cord.[18] Houde and Wikler,[19] however, have found that morphine depressed the skin twitch response in both intact and spinal dogs, the effect being more intense in the former. They concluded that the skin twitch response measured not only the central "analgesic" effect of morphine but also the depression of the drug on a spinal reflex.

Our regression lines showed the two slopes

previously found by Pittinger *et al.*[16] for several anesthetic agents. However, the symptoms exhibited by our rabbits in response to the increased anesthetic concentrations do not allow us to relate slow and steep slopes to "analgesia" and "anesthesia" respectively, as suggested by those authors. Typically, excitement, salivation and loss of corneal reflex occurred at the upper end of the steep slope.

Discussion

The frequent discordances between the results of analgesimetry in man and animal suggest caution in transposing our findings in rabbits to humans and concluding that in man trichlorethylene probably has no specific analgesic effect on the trigeminal nerve.

Prolonged anesthesias of the trigeminal territory have often been attributed to trichlorethylene, in industry as well as in anesthesia.[20, 21] The literature, however, reveals that the specific involvement of the fifth cranial nerve has most often occurred in industry, with an unpurified product, or when decomposition by air, sunlight or soda lime took place.[20, 23] In those cases the product manifested a specific "toxic" rather than "therapeutic" effect. Moreover there is good evidence that other products have to be incriminated.[20, 22]

Along with the above considerations and the experiments of previous authors, the results of the present work cast doubt upon the theory of a specific trigeminal effect of trichlorethylene. They suggest that the theory ought not be accepted without a critical attitude and they invite further investigation.

Summary

We have compared the action of trichlorethylene upon two reflexes in rabbits: the tooth pulp chewing reflex involving the trigeminal nerve and the skin twitch reflex involving a spinal nerve. Chloroform and morphine were also studied by the same methods for comparison. Intensity and duration of analgesia were studied separately. Our results and their statistical computations indicate that trichlorethylene depresses both reflexes with the same intensity and for the same period of time. Chloroform acts in the same manner. Morphine appears to have a more intensive effect on the skin twitch reflex.

These results cast doubt upon the theory of a specific analgesic effect of trichlorethylene and invite further investigation.

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DROWNING Clinical observations suggest that the drowning human sustains a period of laryngospasm before asphyxial relaxation of the glottis allows flooding of the respiratory tract. In dog experiments designed to simulate the features of human drowning intermittent positive pressure breathing (IPPB) consistently resuscitated dogs subjected only to obstructive asphyxia. When the lungs were flooded with fresh water following a period of obstructive asphyxia ventricular fibrillation occurred despite attempted resuscitation with IPPB. After 10 minutes of IPPB resuscitation of dogs whose lungs had been flooded with sea water following a period of obstructive asphyxia, spontaneous respirations occurred, but these animals died quickly in marked pulmonary edema. Likely causes for the consistent mortality following flooding of the lungs include hemolysis and electrolyte changes in the case of fresh water and hypovolemia, hemoconcentration, and changes in plasma electrolyte concentrations with sea water. Artificial respiration with IPPB seems to be effective in resuscitating apneic victims of submersion if they have suffered from laryngospasm only, without flooding of their lungs. (*Redding, J., Voight, G., and Safar, P.: Drowning Treated with Intermittent Positive Pressure Breathing, J. Appl. Physiol. 15: 849 (Sept.) 1960.*)

FAULTY ENDOTRACHEAL TUBE A 33 year old healthy woman was anesthetized for thyroidectomy. An endotracheal tube was inserted and the operation proceeded uneventfully until suddenly the anesthetist was unable to inflate the lungs. Various maneuvers were tried to improve the airway. The cuff was finally deflated and the suction catheter passed. Although no mucus was obtained, the airway was restored. However, by this time hypoxia was so great the patient had cardiac arrest. Cardiac massage was instituted, but the patient died six hours postoperatively. Examination revealed that the cuff on the endotracheal tube inflated unevenly forcing the bevel of the endotracheal tube against the tracheal wall producing complete obstruction. Endotracheal tubes with the least suspicion of weakness or uneven inflation should be discarded. When cardiac arrest is secondary to respiratory obstruction, the brain is already anoxic and the assumption that any safe margin of time exists is invalid. (*Pryer, D. L., Pryer, R. R. L., and Williams, A. F.: Fatal Respiratory Obstruction due to Faulty Endotracheal Tube, Lancet 2: 742 (Oct. 1) 1960.*)