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Pharmacologic Demonstration in Man of Increased Thresholds to Tooth Pain Following Carisoprodol and other Analgesics. (26166)

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Most methods for evoking experimental pain in humans trigger at the same time adjacent sensory fibers which interfere with precise perception and measurement of pain. Brashear(1) has observed that thermal, mechanical or chemical stimulation of a normal human tooth triggers pain only. No other sensation is experienced. Only pain fibers enter the pulp accompanying larger vessels and form an almost complete mantle around the arteries. The practicability of an algesimetric method based upon this neural structure is enhanced by constant conditions of stimulation afforded by a suitable electronic stimulator(2,3,4).

Methods. With a Burton "vitalometer,"* current was delivered to the base of the upper right incisor for 2 seconds, and increased by small increments at 5 to 10 second intervals until unequivocal recognition of pain was reported by the subject. One threshold measurement was made at each hourly trial. The contacting electrode was kept moist by frequently dipping it in 70% alcohol. Twenty normal men and women, 22 to 52 years of age, participated. Neither observer nor subjects had knowledge of the assignments of placebo or drug. One week elapsed between tests. On test days subjects reported to the laboratory at 9:00 a. m., when a control pain threshold record was obtained. Each subject then received 2 capsules of drug or placebo immediately after this test. Every subject received placebo 3 times during the series of trials. No foods or drinks were consumed until after all threshold tests had been completed. One hour after the drugs were ingested a second tooth pulp pain threshold was determined. A final threshold measurement was made 2 hours later (11:00). With initial readings (9:00 a. m.) as baseline, changes in tooth pulp threshold were calculated, and means computed for one-hour and 2-hour intervals. Biometric tests for significance of differences between groups are based upon "F" values derived by the analysis of variance(5).

Results. Carisoprodol at a single oral dose of 350 mg in gelatin capsules produced a statistically significant increase in pain threshold (130 ± 12.7% at one hour; 132 ± 12.4% at 2 hours) (Fig. 1). A single dose of 30 mg of codeine phosphate orally also raised pain threshold (128 ± 8.3% at one hour; 130 ± 10.1% at 2 hours). Placebo response did not differ significantly from baseline thresholds (96 ± 4.2% 104 ± 4.5%). Meprobamate in a single oral dosage of 800 mg failed to show any analgesic effect; the threshold value of 100 ± 7.4% did not differ significantly from placebo or baseline responses. In a single oral dose, acetylsalicylic acid at 1200 mg/person elevated pain threshold significantly at one hour (121 ± 14.5%). This response, however, was of relatively short duration since a statistically significant increase was not found at 2 hours. With 600 mg of acetylsalicylic acid, pain threshold was elevated (109 ± 9.2%), but not significantly. An oral dose

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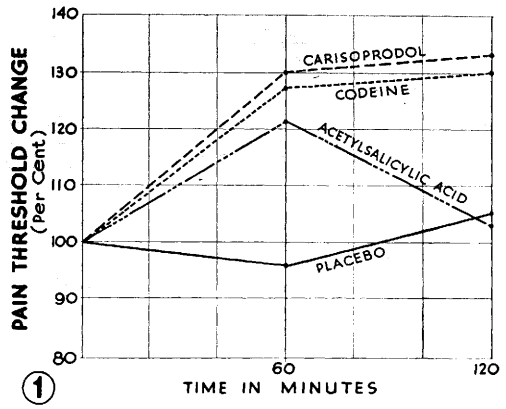

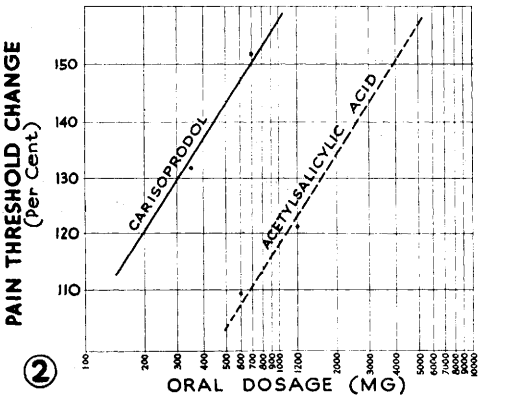

FIG. 1. % changes in tooth pulp threshold of humans following single oral doses carisoprodol (350 mg), codeine phosphate (30 mg), acetylsalicylic acid (1200 mg), or placebo. All preparations administered as capsules identical in appearance.

FIG. 2. Comparison of analgesia in man of carisoprodol and acetylsalicylic acid. Changes in tooth pulp threshold as a function of log-dose of drug.

of 700 mg of carisoprodol given as coated tablets markedly elevated pain threshold (151 ± 20.5% after 2 hours). A comparison of results obtained in this test suggests that carisoprodol was 5.4 ± 1.9 times more potent than acetylsalicylic acid in increasing tooth pain threshold (Fig. 2).

Discussion. Pharmacological studies in rats showed that there is a large ratio between doses of carisoprodol that produce paralysis and those causing insensibility to joint pain. This suggests that carisoprodol might possess significant analgesic properties in addition to being a potent skeletal muscle relaxant(6). Elevation of the tooth pain threshold following administration of carisoprodol was marked. Since the end-point did not require physiological intervention of muscle tissue for contraction, and was derived strictly from stimulation of pain fibers, it must be concluded that carisoprodol, like codeine phosphate or acetylsalicylic acid, acts as a true analgesic. Recently Holliday and Dille(7) described use of an ultrasonic stimulus for inducing deep bone pain in human volunteers. By this procedure, 700 mg carisoprodol orally resulted in a similar statistically significant rise in pain threshold. The intensity and duration of the pain threshold changes for acetylsalicylic acid follow changes in drug blood plasma concentration described by Mandel, *et al.*(8). The peak of response after this drug approximates maximal plasma concentration. The pharmacological response also follows very closely the clinical time-effect curves for acetylsalicylic acid reported by Houde, *et al.*(9). Likewise the response to carisoprodol follows closely the plasma level changes described for this drug. Maximal plasma concentration appears between 2 to 4 hours after oral administration(10).

Neuropharmacological studies by Kletzkin (11) and Longo(12) suggest the analgesic property of carisoprodol possibly derives from an action upon the reticular formation similar to that observed for morphine. Furthermore, the pharmacological demonstration in man of depressed sensitivity to pain involving the 2nd or 3rd divisions of the fifth cranial nerve suggests a clinical potential of carisoprodol for regional headache pain involving these divisions. Mephenesin in large intravenous doses has been reported to depress painful head sensations normally feeding through these divisions(13). Finally, a simple rapid means for assaying analgesic properties in man is afforded by the cited technic, and it seems to merit further trials with other analgesics. Since no significant analgesic action by the placebo can be shown by this method (Fig. 1), it affords a neurophysiological means of directly measuring analgesic action in the human.

Summary. 1. A pharmacological procedure is described which has clearly demonstrated the oral analgesic activity of carisoprodol (350 mg), acetylsalicylic acid (1200

mg), and codeine phosphate (30 mg) in man. Drugs were given with placebos in a "double-blind" investigation. Pain was induced by a high-frequency electronic stimulator applied to normal intact teeth. 2. Since the pain threshold end-point did not require activation of skeletal muscle, carisoprodol must have induced analgesia independently of its muscle relaxant action. 3. By this method, carisoprodol was 5 times more potent than acetylsalicylic acid in raising tooth pain threshold in man.

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Effect of Triethylene Thiophosphoramide (ThioTEPA) on Skin Pigmentation in Mice.* (26167)

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Hyperpigmentation of the skin of man and experimental animals following exposure to ultraviolet light or ionizing radiation is a commonly observed phenomenon. Radiation-induced hyperpigmentation has been shown to result from an increased amount of epidermal melanin associated with increased functional activity of the melanocytes in mouse(1) and human(2) skin. Similar results have been obtained in mice following local application of the carcinogenic hydrocarbon 5, 9, 10 - trimethyl - 1,2 - benzanthracene(3). During cancer chemotherapy studies in mice utilizing triethylene thiophosphoramide (ThioTEPA) it was observed that brown mice of the CBA and (RIII x CBA)F_1 hybrid strains undergoing long-term systemic administration of this drug developed a marked hyperpigmentation of the tail, ears, and extremities, similar to that described in mice exposed to chronic gamma-irradiation (1). The present study deals with the effects of ThioTEPA on skin pigmentation in various inbred strains of mice.

Methods and materials. ThioTEPA is the sulfur derivative of triethylene phosphoramide and is a member of the class of radiomimetic, tumor-inhibitory compounds known as alkylating agents. Dry crystalline ThioTEPA was dissolved in distilled water to make a concentration of 0.25 mg/ml and was refrigerated during the course of the experiment. Nine male and 9 female mice, 50 to 60 days old, of each of the following inbred strains were used:‡ DBA/2, Strong A, C3H, NH, Stoli, and (DBA/2 x NH)F_1 hybrids. Six males and 6 females of each strain were

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