Prolongation and Potentiation of Oral Codeine Analgesia in the Rat.* (24231)

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Although codeine has only moderate oral analgesic properties, it has long been employed particularly in combination with aspirin, phenacetin, and caffeine compounds. Since even such mixtures must be given every few hours for prolonged pain relief, a preparation has been sought which would produce a longer acting and potentiated response. This study describes analgetic activity of codeine complexes and combinations having such properties. In view of findings that drug-resin products dissociate slowly in the G.I. tract causing delayed absorption and prolonged drug action(1,2), codeine has been reacted with synthetic ion exchange resins† to form a resinate complex which appears to have a prolonged duration of action. (Additionally, methylatropine and Tuazole (2-methyl-3-orthotolyl-4-quinazolone) have been found to potentiate the analgesic activity of codeine. Other quinazolones (including halogen derivatives) are under investigation. These drugs form reaction products with synthetic ion exchange resins which likewise show prolonged action *in vivo*.

Methods. The D'Amour and Smith(3) apparatus and technique for analgesiometric measurement in the rat was used with a 300 watt AC projection lamp at 95-100 volts as a heat source. Two groups of 10 animals each were placed in the dolorometer and their response time measured. The voltage was adjusted so that mean baseline response time was of the order of 2 sec. The voltage was then kept constant throughout the experimental period. The pre-treatment response time of each animal was measured 3 times. The average of second and third values was taken as the animal's baseline response time. Drugs were given by gavage as aqueous solutions or suspensions at a 5% dose volume. Response time was measured 30 min. after dosing and then at intervals usually 1 hour apart. Ten sec was the maximal stimulus time in any measurement. For each animal, baseline response time was subtracted from each post-dose response time (= Δ sec). This value less 3 Δ sec (the criterion of minimum analgesia) was multiplied by hours elapsed after administration of the dose (= Δ sec hr) and totaled (Σ Δ sec hr) for each animal. The mean and stand. dev. of Σ Δ sec hr of test and control groups were calculated. "Students t" test was used to demonstrate whether the difference of the means was statistically significant.

Results. Reproducibility of analgesic measurements. (1) Rat-to-rat variation is large as evidenced by large stand. dev. (2) day-to-day variation is greater than dose-to-dose variation (Table I). Accordingly, a reproducible log dose-effect curve could not be derived. Each test is a 1 x 1 direct comparison.

Codeine sulfate. 50 mg/kg of codeine showed effective analgetic response (greater than 3 Δ sec) at 30 min but not after 90 min. At 75 mg/kg potency was similar but effec-

TABLE I. Measurement of Analgesic Activity of Codeine Sulfate.

Dose, mg/kg (as codeine)	Date	$\bar{\Sigma}$ (Δ sec.–3) hr	No. of rats
50	7/15/57	7.64 ± 8.7	10
	9/ 3	1.79 ± 3.5	9
	6	5.53 ± 9.5	8
	13	1.78 ± 5.2	9
	10/ 3	2.15 ± 3.2	4
	11	17.73 ±20.0	8
	24	7.40 ± 7.7	3
	25	13.60 ±12.6	5
	12/ 4	2.82 ± 5.4	10
	3/ 3/58	17.21 ±13.1	10
	Mean	7.76	
75	7/ 2/57	17.88 ±20.3	5
	3	16.56 ±20.8	5
	Mean	17.17	

* A preliminary report of this work was given at the Fed. Am. Soc. Exp. Biol., April, 1958.

† The sulfonic acid cation exchangers Amberlite IR-120 and XE-69 were used.

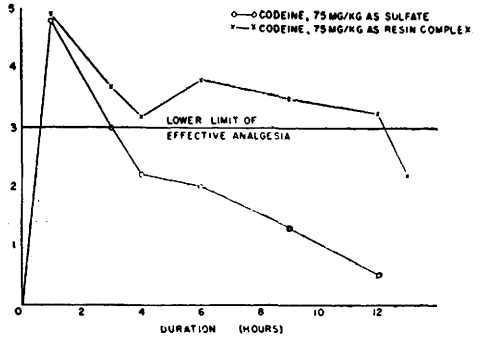

FIG. 1. CODEINE ANALGESIA IN THE RAT. PROLONGATION BY RESIN COMPLEX.

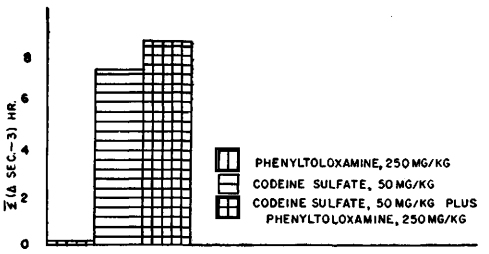

FIG. 2. EFFECT OF PHENYLTOLOXAMINE ON CODEINE ANALGESIA

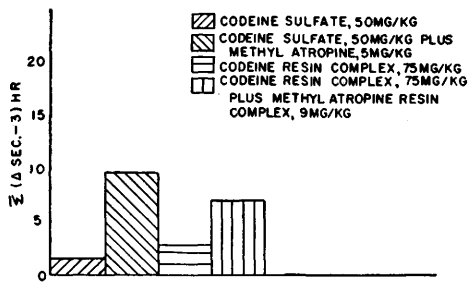

FIG. 3. POTENTIATION OF CODEINE ANALGESIA BY METHYL ATROPINE.

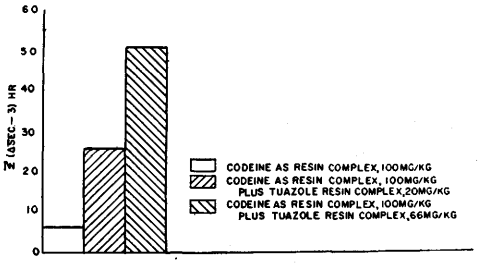

FIG. 4. POTENTIATION OF CODEINE ANALGESIA BY TUAZOLE.

FIG. 1-4.

tive analgesia lasted 90-180 min (Fig. 1).

Codeine resinate. 75 mg/kg produced effective analgesia equal in intensity to that of 50 mg/kg of codeine as sulfate, but of much longer duration (4-12 hr) than that of even 75 mg/kg of codeine as sulfate. Hence, prolongation of effect is attained.

Codeine potentiators. Phenyltoloxamine, coadministered in doses up to 250 mg/kg did not enhance the analgetic activity of 50 mg/kg of codeine as sulfate (Fig. 2). Methylatropine (Metropine‡) at 5 and 10 mg/kg as the nitrate enhanced the analgetic action of 50 mg/kg of codeine as sulfate. 9 mg/kg of methylatropine as resinate potentiated the analgetic effect of 75 mg/kg of codeine as resinate (Fig. 3). Tuazole, which has no analgetic properties, in a dose of 20 mg/kg increased the analgetic activity of 50 and 100 mg/kg of codeine as sulfate. When both codeine (100 mg/kg) and Tuazole (20 mg/kg) were given as resinates, the analgesic activity was increased by an average factor of 4.3. Increase of the Tuazole dose to 66 mg/kg increased the factor to 6.4 (Fig. 4).

Discussion. Prolongation of therapeutic activity of a number of drugs has now been achieved by reacting them with appropriate synthetic ion exchangers(1,2). Where the drug resinate exhibits prolongation of action, it is less toxic than the soluble salt form when compared on a "free" drug basis(4).

The D'Amour-Smith rat analgesiometric technic as a means of predicting analgesic drugs has been criticized because of the difference in metabolism of codeine in rat(5) and man, and the persistence of the tail flick reflex after spinal section. Nevertheless, Beecher concluded that the D'Amour-Smith technic was useful in evaluation of potential analgesics(6).

There is no agreement as to treatment of data obtained by the D'Amour-Smith technic. Some workers employ an all-or-none basis for

‡ R. J. Strasenburgh Co. registered trademark for methylatropine nitrate.

evaluation while others treat data as graded responses(7). We have employed a combination of quantal and graded response criteria. Three Δ sec change in response time is used as an all-or-none criterion for establishment of adequate analgesia. Pain in man is a graded sensation. Therefore, it would appear reasonable to treat responses greater than 3 Δ sec in the rat as graded responses. The use of a 10 sec cut-off time introduces bias into the treatment of graded responses(8). However, values above 10 sec would be interpreted as having greater analgetic potency and thus in this case the bias increases conservatism in predicting the efficacy of new analgetics.

Duration, as well as intensity of effect, becomes a problem in evaluation of long-acting drugs. Winter(9) has suggested a simple means. However, the calculation employed above is considered an improvement in that it gives greater weight to duration than to degree of analgetic.

Successful potentiation of oral codeine analgesia by non-analgetic drugs has not, to authors' knowledge, previously been accomplished. Prostigmine was claimed to potentiate codeine but this finding was not confirmed. Solanaceous alkaloids have been claimed to depress intensity and duration of morphine effects(6). The evidence presented here shows that methylatropine potentiates codeine analgesic. The combinations of codeine with methylatropine and with 2-methyl-3-orthotolyl-4-quinazolone, all as ion exchange resin complexes are now undergoing clinical evaluation. Preliminary reports indicate that each of the combinations possesses enhanced analgetic potency and duration of effect(10).

Summary. 1. The reaction product of codeine and appropriate synthetic ion exchange resins has been demonstrated to possess analgetic properties of codeine. The resin-complex has a longer duration of action than does soluble forms of the drug. 2. Codeine analgesia has been potentiated by methylatropine and 2-methyl-3-orthotolyl-4-quinazolone. Both the resin complex and soluble salt forms of codeine are potentiated by these agents. 3. Resin reaction products of methylatropine and 2-methyl-3-orthotolyl-4-quinazolone have been prepared. Both of the drug resin combinations exhibit prolongation of action, including the property of codeine potentiation, the latter drug beng more potent in this respect. 4. Combinations of codeine-resin complex and of methylatropine or 2-methyl-3-orthotolyl-4-quinazolone in resin complex form are potent, long acting analgesics in the rat. 5. Analgesiometric data obtained in the rat by the D'Amour-Smith method have been treated so as to express both duration and intensity of action. More weight is given to duration of adequate analgesia than to intensity of analgesia.

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