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Toward the Development of a Potent, Nonsedating, Oral Analgesic

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Abstract. The separate and combined analgesic effects of 10 mg of oral amphetamine sulfate and 25 mg of oral anileridine dihydrochloride were studied in 24 healthy, adult, male volunteers. Tolerance of progressively increasing pain produced by the Submaximum Effort Tourniquet Technique was tested four times in each subject: after amphetamine, after anileridine, after the combination, and after a matching placebo. Treatments were administered double blind and in counterbalanced order. Elapsed time to report of slight, moderately distressing, very distressing, and unbearable pain was recorded on each trial. The four oral treatments differed significantly for very distressing and for unbearable pain. At each of the three upper pain levels, the mean tolerance times for anileridine and amphetamine were similar; each was longer than placebo but shorter than the combination; and the effect of the combination was approximately the sum of the effects of the two components.

Key words: Experimental pain – Analgesics – Anileridine – Amphetamine

In 1944, Ivy and his colleagues first reported on the synergy between an opiate and an amphetamine for analgesia (Ivy et al., 1944; Goetzl et al., 1944a, b). Three years previously, DeVoine (1941) had noted that in patients with a coronary occlusion such a combination reduced vomiting, mental depression, and other untoward side effects of opiates. Thereafter, several authors presented evidence regarding improved analgesia and reduced side effects when such drugs were combined (Nickerson and Goodman, 1947; Abel et al., 1951; Saxena and Gupta, 1957; Milosevic, 1958; Sigg et al., 1958; Witkin et al., 1961; Evans, 1962). The first controlled clinical trial of this type of mixture was reported by Evans (1967). Although the number of patients was small, the results indicated a significant increase in analgesia with concomitant reductions in such side effects as sedation, lowered blood pressure, and vomiting. Recently, Forrest et al. (1977) found that supplementing intramuscular morphine with intramuscular dextroamphetamine enhanced the relief of postoperative pain and offset morphine-induced impairment of alertness.

The present study provides further information concerning the analgesic effects of amphetamine combined with a narcotic in an experimental design in which all drugs were administered orally and pain was induced experimentally. This study also provides information concerning the analgesic effect of oral amphetamine administered alone and oral anileridine administered alone. Finally, it extends information concerning the usefulness of the Submaximum Effort Tourniquet Technique for assessing analgesic potency (Smith et al., 1966, 1968; Smith and Beecher, 1969).

The narcotic anileridine was chosen for this study because of its remarkable oral effectiveness. The oral dose is said to be exactly the same as the parenteral for equivalent analgesia (Wallenstein and Houde, 1959). Anileridine (ethyl-1,-4 aminophenylethyl-4 phenylisonipecotate) is a derivative of meperidine in which a phenethyl group has been substituted for a methyl group in the meperidine molecule, with the same peak effectiveness, degradation, and general metabolism (Weijlard et al., 1956; Orahovats et al., 1957). Along with its enhanced oral potency, anileridine is also reputed to have less sedating side effects than meperidine (Weijlard et al., 1956; Orahovats et al., 1957). Wallenstein and Houde (1958) equated 30 mg anileridine i.m. with 80 mg meperidine and 10 mg mor-

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phine in analgesic potency. The addiction liability of an opiate-amphetamine mixture was examined in animals by Deneau (1970) and in humans by Jasenski and Nutt (1972). Their reports suggest that in equianalgesic doses the addiction liability of such mixtures is similar to that of opiates alone.

Materials and Methods

The submaximum Effort Tourniquet Technique (Smith et al., 1966, 1968; Smith and Beecher, 1969) was used to produce pain in each of 24 healthy Army enlisted men who ranged in age from 19 to 40 (median = 23 years) and whose average weight was 82 kg.

Informed, written consent was obtained from all subjects. The Army medical record was reviewed, a special health questionnaire was administered, a medical history was taken, and a physical examination was performed by a physician not otherwise connected with the study. Volunteers were not accepted into the study if they reported having used drugs for medical or nonmedical purposes during the month preceding their interview and examination. Volunteers with a history of allergic responses were also excluded.

After a practice trial was performed to familiarize each subject with the test procedures, the subject was given four experimental trials: once after taking anileridine dihydrochloride (25 mg), once after amphetamine sulfate (10 mg), once after taking both drugs, and once after placebo. Each medication was administered orally 90 min before production of pain was initiated on any particular experimental trial. Use of a two-capsule procedure made the four drug treatments visually indistinguishable. Drug order was counterbalanced and double blind.

The following procedure was used to produce ischemic pain in the arm and to evaluate its intensity. The subject reclined on a bed and extended his nondominant arm toward the ceiling. An Esmarch bandage was used to drain the arm of venous blood. Immediately before removal of the Esmarch bandage, a 3-inch band pneumatic tourniquet, placed around the subject's upper arm, was inflated to a pressure of 250 mm Hg. The subject then lowered his arm to his side and, after a pause of 60 s, squeezed a hand-spring exerciser 20 times while his arm rested on the bed. Each squeeze was timed to last 2 s, followed by a 2-s rest. This schedule was presented to the subject by means of tape-recorded signals. When the exerciser was squeezed to the point at which the handles touched, and no further movement was possible, a light came on and remained on as long as the handles were in contact. Thus the subject and experimenter both knew when a squeeze failed to reach the criterion (handles touching for 2 s). Subjects were not disqualified for slight variations in meeting this criterion, but before his first session, each volunteer was told that his acceptability as a subject depended on his maintenance of a cooperative and responsible attitude.

The hand-spring exerciser used has an excursion distance of 4.2 cm and requires 7.72 kg of pressure to bring the handles together. In studies of over 300 healthy adult male subjects, none has proved incapable of completing 20 squeezes with the tourniquet inflated. In such a population, 20 squeezes do not require a maximum effort. It is this characteristic of our version of the ischemic-pain procedure that gives rise to its name. The logical and methodological advantages of the Submaximum Effort Tourniquet Technique were discussed in detail when the method was introduced by Smith et al. in 1966. Briefly, those advantages are: (1) It reduces the number of squeezes, thereby preventing fatigue and cramping from being confounded with the end-point for pain tolerance; (2) it holds the required number of squeezes constant from trial to trial, so that neither drug-induced fatigue nor drug-induced elevation of pain threshold can alter the pain stimulus; and (3) it increases pain duration, thereby making the experience resemble pain of pathologic origin more closely.

After completing 20 squeezes, the subject remained in a reclining position and rested his arm at his side with the tourniquet still inflated. After cessation of squeezing, ischemic pain in the arm increased progressively until the subject reported it to be 'unbearable' – at which point the experimenter removed the tourniquet and thereby stopped the pain.

During the period of progressively increasing pain, the subject was asked, at irregularly spaced intervals, to rate his pain on a 5 point scale: 0 = none, 1 = slight, 2 = moderately distressing, 3 = very distressing, 4 = unbearable. Irregular intervals were used to minimize cues to the subject regarding the length of time he had tolerated the pain. The investigator, stationed in an adjoining room, requested ratings over an intercommunication system 0, 3, 5.5, 9.5, 10.5, 14, 16, 17.5, 21.5, 22.5, 26, 28.5, 30, 33, 35, 37, 39.5, 42.5, 43.5, 47, 48.5, 52.5, 56.5, 59.5, and 60 min after cessation of exercise, unless the trial was terminated earlier by the subject's report of unbearable pain. For reasons of safety, no trial is ever allowed to exceed 60 min, but none of the trials in this particular experiment reached that limit. The latest report of pain level 4 was at 53.6 min, the earliest was at 8.0 min, and 73% of the level-4 ratings fell in the range of 15–45 min.

Results

Table 1 reports the mean tolerance time for each of four pain levels under each of the four experimental conditions (placebo, amphetamine, anileridine, and amphetamine plus anileridine). Note that for all criteria except slight pain, anileridine and amphetamine have similar tolerance times, both have longer times than placebo, and the time for the combination is longer than that for either active drug alone. Note also that for the three upper pain levels, the effect of the combination was approximately the sum of the effects of the two components. For example, at the highest pain level, the amphetamine-placebo difference was + 5.2, the anileridine-placebo difference was + 6.6, and the difference between the combination and the placebo was +11.3. Analyses of variance showed that the four drug treatments gave a significant F-ratio for level 4 ($P < 0.001$) and level 3 ($P < 0.01$), but not for level 2 or level 1.

Table 1. Mean duration (in min) of tourniquet stimulation required to produce each of four levels of pain under each of four treatment conditions

Pain level	Placebo	Amphetamine	Anileridine	Amphetamine and anileridine
Unbearable	22.8	28.0	29.4	34.1
Very distressing	17.5	21.4	21.4	24.5
Moderately distressing	11.5	12.9	13.8	15.5
Slight	4.3	2.6	3.8	4.4

Table 2. Effects of drugs on tolerance times for each of four pain levels: mean differences in minutes

Drug effects	Unbearable	Very distressing	Moderately distressing	Slight
Amphetamine alone (amphetamine minus placebo)	+5.2	+3.9	+1.4	−1.7
Amphetamine added to anileridine (combination minus anileridine)	+4.7	+3.1	+1.7	+0.6
Anileridine alone (anileridine minus placebo)	+6.6	+3.9	+2.3	−0.5
Anileridine added to amphetamine (combination minus amphetamine)	+6.1	+3.1	+2.6	+1.8
Amphetamine and anileridine (combination minus placebo)	+11.3	+7.0	+4.0	+0.1
Standard error[a]	±2.11	±1.93	±1.50	±0.93

[a] These standard errors were computed from the analysis of variance appropriate to the crossover design (Cochran and Cox, 1950)

Table 2 shows the same relationship among means that are revealed in Table 1, but it does so from the perspective of mean differences rather than means, and it provides standard errors by which those differences can be assessed. As seen in Table 2, the drug effects are most distinct for pain level 4, the final end-point. The results for that end-point indicate (1) that 10 mg of amphetamine significantly prolongs tolerance of tourniquent pain, and that the prolongation due to amphetamine is approximately 5 min whether the drug is given alone or with anileridine; (2) that 25 mg of anileridine significantly prolongs tolerance (approximately 6 to 6.5 min whether given alone or in combination with amphetamine; and (3) that the analgesic effects of amphetamine and anileridine are similar to each other and are approximately additive.

At pain-level 3, the results are smaller and less significant than those at level 4. The combination is significantly different from placebo, and each component is also significantly different from placebo; but the effect of adding one component to the other is not statistically significant.

At pain-level 2, the only significant difference is between the combination and placebo. At pain-level 1, no difference is significant.

The combination was significantly superior to placebo at pain-levels 4, 3, and 2; and although it tended to be superior to each component at all pain levels, that superiority was statistically significant at only the final end-point, i.e., at pain-level 4.

Discussion

For the final end-point of pain produced by the Submaximum Effort Tourniquet Technique (unbearable pain), both 10 mg of amphetamine sulfate and 25 mg of anileridine dihydrochloride prolonged pain tolerance significantly; moreover, the effect of the combination of amphetamine plus anileridine was significantly greater than that of either component alone, and it was approximately the sum of their separate effects. Discrimination among the drug treatments at lower levels of pain was less successful. Here, as in earlier studies reported by Smith et al. (1966, 1968; Smith and Beecher, 1969), the Submaximum Effort Tourniquet Technique proved sensitive to the effects of known analgesics. In the present study, as in the earlier ones involving narcotic analgesics (1966 and 1968), discriminative power was more dependable at the higher than at the lower pain levels produced by the method.

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