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Qualitative Differences in Effects of Opioids in Man: Preliminary Evidence for Multiple Mechanisms of Analgesic Action

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ABBOTT, F. V. *Qualitative differences in effects of opioids in man: Preliminary evidence for multiple mechanisms of analgesic action.* PHARMACOL BIOCHEM BEHAV **24**(5) 1247–1251, 1986.—The analgesic effects of meperidine, anileridine, codeine and codeine + acetominophen on surgical and non-surgical pain in 101 patients were assessed using the McGill Pain Questionnaire. The quality of analgesia was determined by analyzing the changes in the pain descriptors chosen 1 hour after medication. Meperidene and anileridine differentially reduced pain qualities rated as "bright-phasic" by a student sample. Codeine and codeine + acetominophen produced similar patterns of analgesia that were homogenous across "bright-phasic" and "dull-tonic" types of pain. The data suggest the possibility that opioids may differ in the quality of analgesia produced either as dose increases or different opioid receptor types are recruited.

Opioids Analgesic action Quantitative differences Meperidine Anileridine Codeine

BEECHER [3] suggested many years ago that opiate analgesia was primarily dissociative in nature and was exemplified by a patient reporting "the pain is still there but it no longer bothers me." On the other hand, recent studies on the mechanisms of action of opioids indicate that a major mechanism of action is to inhibit nociceptive sensory afference (for reviews, see [3,10]). Consistent with the latter, epidural morphine appears to have a relatively specific profile of analgesic effects in that deep continuous somatic pain is more effectively relieved than intermittent or visceral or cutaneous pain [1].

The present report is a reexamination of a data base, collected for other purposes, in which information on the quality of analgesic effects of three opioids is embedded. Pain was assessed using the McGill Pain Questionnaire (MPQ; [16,17]) before and one hour after analgesic medication. The MPQ is interesting in this context because it assesses pain quality and is able to discriminate among a number of pathological conditions on this basis [6, 21, 22]. In addition, the MPQ assesses both the sensory quality and the affective-evaluative response to pain with a moderate degree of independence [20, 22, 26]. The questionnaire may, therefore, be able to yield information on the nature of opioid analgesia in man.

METHOD

Sample

The subjects were 101 patients in surgical wards of a general hospital. Eighty-six percent had undergone surgery within the past 14 days (elective amputation, cholecystectomy thyroid lobectomy, lung lobectomy, hernia, colectomy, laminectomy/discoidectomy, other). The remainder were patients with non-surgical pain, primarily of neoplastic origin. This diverse sample had the advantage that many pain qualities were well represented.

Procedure

The procedure was as follows. A research assistant waited at the nursing station until a patient requested analgesic medication. The study was then explained to the patient and if he/she agreed to participate, a pain questionnaire was administered at that time and again 1 hour after an analgesic agent was administered by the nurse. This procedure selected patients who were in pain and who had not received medication for pain for at least 4 hours. No attempt was made to influence the drug or dose which the nurse administered on the basis of standing PRN orders because the original purpose was to obtain information about patterns of medication use.

The data reported here are for four groups of patients, those who received 75 or 100 (mean=90.5) mg meperidine IM; 25 or 37.5 (mean=28.9) mg anileridine IM; 30 or 60 (mean=41.2) mg codeine PO; and 30 or 60 (mean=36.8) mg codeine plus 650 mg acetominophen PO. For a subsample of the patient population (n=84) body weights were available and there was a significant correlation ($r=.29$, $p<0.01$) between body weight and dose when doses are scaled according to drug equivalents [11]. This and the two-fold or lower dose range justify treating each of the four drug groups as a whole rather than attempting a dose-effect analysis.

Pain Assessment

Pain was assessed using McGill Pain Questionnaire (MPQ) shown in Table 1. The MPQ consists of a list of 80 words that describe qualities of pain. They are arranged into

20 categories which reflect a particular pain quality [17]. These 20 categories are usually grouped to yield 4 scores: sensory, affective, evaluative and miscellaneous [16].

An alternative scoring technique is to use the scaled intensity values (Table 1) determined by Melzack and Torgerson [17] to yield a score on a scale from 0 to 5 for each category. This method was applied to the data by determining the proportion of patients using each word for the pre- and post-drug tests. A pre- and post-drug weighted pain value (WPV) for 19 of the 20 categories was then calculated as the intensity value for each word multiplied by the proportion of patients using that word. Category #19 ("cool," "cold," "freezing") was not used becuase very few patients chose these words. For example, in category 2, jumping=2.60, flashing=2.75, and shooting=3.42. If 20% of patients chose no word in category 2, 10% chose "jumping," 50% "flashing" and 20% "shooting," then WPV = $((0\times20) + (2.60\times10) + (2.75\times50) + (3.42\times20))/100 = 2.32$.

Qualitative Analysis of the MPQ

Inspection of the MPQ (Table 1) suggests that the sensory words (word classes 1–10, 17–18) can be categorized as "bright-phasic" or "dull-tonic." A group of 16 graduate students were asked to categorize each of the 12 sensory MPQ categories as "bright-phasic" or "dull-tonic." They were instructed to consider the groups of words as a whole and to guess if they did not perceive a clear distinction—i.e., a forced choice task (see Results, Fig. 1A).

Statistical Analysis

The patterns of pain and pain reduction were analyzed using the rankings of the 19 MPQ categories. Where multiple comparisons were made, the α level was adjusted for the number of comparisons in the set using the Bonferoni approach [19] (e.g., for 4 comparisons, if $\alpha\times4<0.05$, then the comparison is considered significant). The adjusted α levels are reported in the text.

A repeated measures ANOVA was used to analyze MPQ scores computed by conventional scoring methods. Because variances were nonhomogenous and correlated with the means, Fs are reported for square root transformed scores.

RESULTS

The pain scores before and after medication using the conventional scoring techniques [16] are shown in Table 2. These scores represent moderate to severe pain [16]. There are no significant differences between the four groups in terms of pain magnitude, $F(3,97)=1.19$; $p>0.1$, or pattern (drug × PRI interaction), $F(3,97)=1.94$; $p>0.1$. The degree of analgesia achieved using the conventional scoring technique is also similar, $F(3,97)=1.84$; $p>0.1$.

The pre-medication weighted pain values (WPV see the Method section) for the four groups were also very similar (r's .79 to .89; W=8.24, $\chi^2=59.36$, $df=18$, $p<0.001$; [8]) and are shown averaged across the four groups in Fig. 1A.

Figure 1B shows the % reduction of the WPVs one hour after meperidine, anileridine, codeine or codeine-acetominophen was administered. The decreases range from less than 20% to 100%. Inspection of Fig. 1A and B indicates that the magnitude of the decrease in the WPVs was not determined by the premedication WPVs. Statistical analysis supports this although in the case of anileridine there was a significant inverse relationship between the premedication WPVs and the magnitude of the decrease (meperidine r=.12, ns; anileridine r=−.54, $p=0.032$; codeine r=.18, ns; codeine-acetominophen r=.15, ns).

Comparison of the pattern of pain reduction produced by meperidine with that of anileridine in Fig. 1B indicates that they are very similar (r=.56, $p=0.042$). The pain reduction patterns produced by codeine and codeine plus acetominophen are also marginally related (r=.53, $p=0.06$). In contrast, the relationships between the pattern of pain reduction produced by meperidine and codeine or codeine-acetominophen were weaker (r=.41, $p=0.23$; r=−.03,

TABLE 1
McGILL PAIN QUESTIONNAIRE

	Scale Value		Scale Value
1. Flickering	1.89	10. Tender	1.35
Quivering	2.50	Taut	2.36
Pulsing	2.56	Rasping	2.61
Throbbing	2.68	Splitting	3.10
Beating	2.70	11. Tiring	2.42
Pounding	2.85	Exhausting	2.63
2. Jumping	2.60	12. Sickening	2.75
Flashing	2.75	Suffocating	2.45
Shooting	3.42	13. Fearful	3.30
3. Pricking	1.94	Frightful	3.53
Boring	2.05	Terrifying	3.95
Drilling	2.75	14. Punishing	3.50
Stabbing	3.45	Gruelling	3.73
Lancinating	3.50	Cruel	3.95
4. Sharp	2.95	Vicious	4.26
Cutting	3.20	Killing	4.50
Lacerating	3.64	15. Wretched	3.16
5. Pinching	1.95	Blinding	3.45
Pressing	2.42	16. Annoying	1.89
Gnawing	2.53	Troublesome	2.42
Cramping	2.75	Miserable	2.85
Crushing	3.58	Intense	3.75
6. Tugging	2.16	Unbearable	4.42
Pulling	2.35	17. Spreading	3.30
Wrenching	3.47	Radiating	3.38
7. Hot	2.47	Penetrating	3.72
Burning	2.95	Piercing	3.78
Scalding	3.50	18. Tight	2.25
Searing	3.68	Numb	2.10
8. Tingling	1.60	Drawing	2.53
Itchy	1.70	Squeezing	2.35
Smarting	2.00	Tearing	3.68
Stinging	2.25	19. Cool	1*
9. Dull	1.60	Cold	2*
Sore	1.90	Freezing	3*
Hurting	2.45	20. Nagging	2.25
Aching	2.50	Nauseating	2.74
Heavy	2.95	Agonizing	3.20
		Dreadful	4.11
		Torturing	4.53

Word classes: 1–10 sensory; 11–15 affective; 16 evaluative; 17–20 miscellaneous.

Pain may be calculated according to the rank of each work in its category or by the scale value of each word on a scale of 0 to 5 [16].

*Arbitrary values.

TABLE 2

MEAN MPQ PAIN RATING INDICES (SD) FOR EACH DRUG GROUP PRIOR TO MEDICATION AND THE MEAN DOSE OF THE DRUGS

	Sensory	Affective	Evaluative	Miscellaneous
meperidine	16.6 (6.1)	2.7 (1.6)	3.0 (1.3)	5.4 (3.3)
anileridine	13.9 (6.0)	2.6 (2.2)	2.3 (1.6)	3.4 (2.5)
codeine	15.6 (7.7)	3.1 (3.4)	2.0 (1.5)	4.9 (3.6)
codeine-acetominophen	14.7 (6.7)	3.2 (2.9)	2.4 (1.6)	4.4 (2.9)

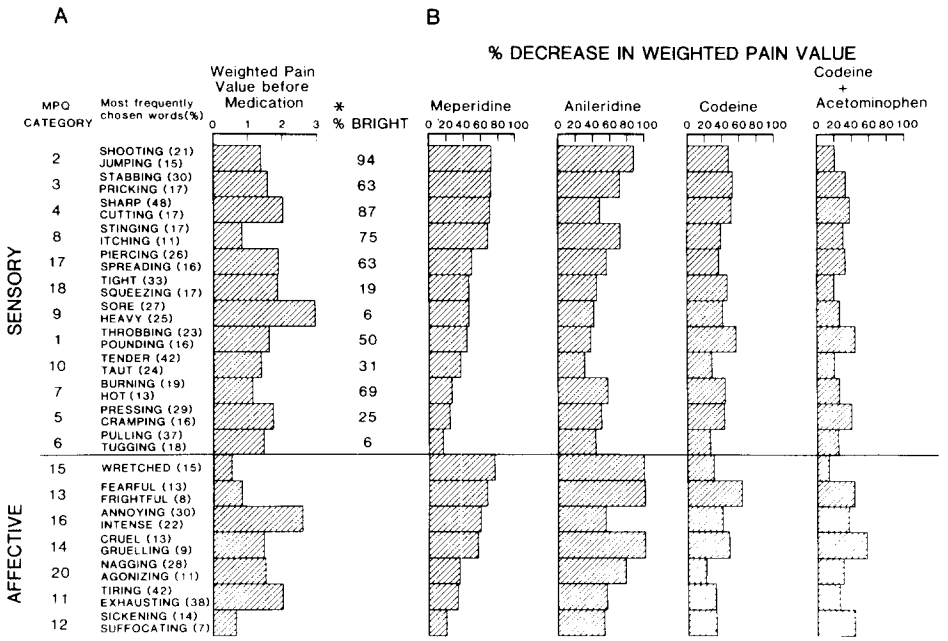

FIG. 1. A. The most frequently chosen MPQ words and the weighted pain value for each MPQ category prior to medication. The MPQ categories have been arranged in order to separate word classes with sensory and affective evaluative connotations and to reflect the pattern of pain reduction produced by meperidine. The percentage of students who rated a category as "bright-phasic" as opposed to "dull-tonic" is also shown. B. The percent decrease in weighted pain value for each MPQ category by meperidine, anileridine, codeine, and codeine + acetominophen.

$p>0.9$). Similarly, anileridine was also dissimilar from codeine and codeine-acetominophen (r=.12, $p>0.9$; r=.11, $p>0.9$).

All four drugs produce analgesia that was reflected in the sensory and the affective-evaluative MPQ word classes. Within the sensory MPQ categories, meperidine and anileridine appear to reduce bright aspects of pain more than dull ones. Thus, "shooting," "stabbing" and "sharp" were markedly more affected than "pulling," "pressing" and "sore." This impression was confirmed in that the % of graduate students rating a word category "bright-phasic" as opposed to "dull-tonic" (Fig. 1A) correlates significantly the degree of reduction for meperidine (r=.65, $p=0.04$) and marginally for anileridine (r=.63, $p=0.056$). In contrast, no such correlation was found for codeine (r=.26, ns) or codeine-acetominophen (r=.11, ns).

In the affective-evaluative word classes, meperidine and anileridine were also different from codeine and codeine-acetominophen. Overall, the former two agents were clearly more potent but this is not reflected equally in all the word categories. Feelings of being "wretched," "fearful" or "annoyed" were greatly relieved by meperidine and anileridine. Both codeine and codeine-acetominophen produced a weaker effect that was more homogenous, as they did in the sensory categories.

DISCUSSION

The data presented here support experimental evidence that major opioids have specific effects on sensory properties of pain (for reviews, see [2,10]). Therapeutic doses of meperidine and anileridine produced marked decreases in "bright-phasic" sensory qualities of pain as well as some of its affective aspects. Codeine, with and without acetominophen, produced analgesia that was remarkably even across the MPQ categories. This pattern would be con-

sistent with Beecher's dissociative analgesia [3] or with a general decrease in all sensory components of pain. The differences in the patterns of analgesia observed were not due to differences in either amount or pattern of premedication pain.

There are two possible explanations for the differences between meperidine and anileridine and codeine. First, on the basis of drug equivalents [11], the doses of codeine were lower than those of meperidine and anileridine. It may be that the decreases in the "bright-phasic" qualities of pain occur at higher doses of opioid drugs, possibly because activation of spinal opioid receptors occurs at higher doses (cf. [28]). Second, there is some evidence in animal studies that meperidine and anileridine are pharmacologically different from morphine [4, 13, 14, 25]. Codeine's analgesic effects are believed to be due to *in vivo* demethylation to form morphine [9]. Clinical support for the differences comes from the observation that meperidine is more effective than morphine for the sharp pain of biliary spasm although the basis of this difference is not established.

The strong similarity between meperidine and anileridine in the present study provides a measure of validity and reliability of this use of the MPQ. These two drugs produce similar effects in behavioral tests in animals. These behavioral effects are pharmacologically distinct from those of morphine and fentanyl in that they are attenuated by pentobarbital and less sensitive to antagonism by naloxone [13,14] and nalorphine [4,25].

The fact that codeine and codeine-acetominophen are so similar in both the pattern and magnitude of the analgesic effects is puzzling. It would be expected that the combination would produce greater and different analgesia on the basis of conventional pharmacological practice. There is, however, a recent paper [24] that compared acetominophen with codeine-acetominophen and found that the combination was actually inferior in pain following extraction of impacted 4th molars: It increased the number of unpleasant side-effects without increasing the amount of analgesia. The present data suggest that codeine dominates the pattern of analgesia when it is given with acetominophen. Whether differences in analgesia between codeine itself and acetominophen can be demonstrated is unclear.

The present study was conducted open and without a placebo control. The analgesia observed, however, is unlikely to include a large placebo component. Most patients had received multiple prior doses of the drug administered at the test time. If the drug had been pharmacologically ineffective, its analgesic effect would have decreased since repeated administration of a placebo tends to produce rapid "tolerance"[7]. If, indeed, placebo effects account for the findings, it would imply that oral and parenteral placebos produce qualitatively different effects whereas to date they have only been shown to differ quantitatively.

The question of open vs. double blind assessment of drug effects is an important one. In the present case, at the time the data were collected the analysis reported here was not conceived and the major objective was to study hospital routine. The findings are unexpected in that morphine has long been reputed to have a greater effect on dull pain than bright pain [5,11]. Therefore, the differential effect of the synthetic opioids, meperidine and anileridine on bright components is unlikely to have resulted from preconceived bias. It should also be noted that blindness is hard to maintain in studies involving narcotic drugs and a research assistant can usually guess group membership accurately in animal tests even when doses are low.

If the proposition that meperidine and anileridine differ from codeine is accepted, then the possible basis of the differences is an interesting question. Opioids produce analgesia in animals by both mu- and kappa-receptor mediated mechanisms [23, 27, 30] and there is evidence that a kappa mechanism may be located in the spinal cord [30]. Codeine itself is a very weak agonist at mu and kappa receptors [12]. Its analgesic activity is believed to be due to *in vivo* demethylation to form morphine [9], a prototypical mu agonist [29]. One speculative interpretation, therefore, is that the undifferentiated pattern of analgesia produced by codeine is similar to what morphine produces. Conversely, the meperidine and anileridine may have relatively more kappa activity which might confer the tendency to reduce bright components of pain selectively. Competitive binding experiments provide some support for this although the relative potency of morphine and meperidine differ by only about 3-fold in their kappa binding relative to their mu binding [15]. A second possible pharmacological difference between morphine and meperidine is that morphine may be unique in increasing spinal serotonin metabolism [31]. Meperidine was not included in this study but several other putative mu agonists were.

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