Pain, 39 (1989) 249–256
Elsevier

PAIN 01484

Clinical Section

Comparison of subjective and objective analgesic effects of intravenous and intrathecal morphine in chronic pain patients by heat beam dolorimetry

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(Received 6 April 1988, revision received 9 June 1989, accepted 12 June 1989)

Summary The pain tolerance latencies of 10 chronic pain patients were evaluated by heat beam dolorimetry (stimulus intensity 15.33 $mW \cdot cm^{-2} \cdot sec^{-1}$) prior to and following administration of morphine by intrathecal (n = 5) or intravenous (n = 5) routes. Patients not undergoing opiate withdrawal evinced increased baseline pain tolerance latencies prior to drug administration compared with normal volunteers. Two patients undergoing the opiate withdrawal syndrome at the time of test experienced reduced pain tolerance latencies compared with normal volunteers, most probably corresponding to the hyperesthesia symptom of the syndrome.

Intravenous morphine infusion (30 mg) induced a time-dependent increase in cutaneous pain tolerance with peak effect occurring 1–2 h after administration. This persisted for up to 4 h and thereafter declined. The time course of subjective pain self-report by visual pain analog scale (VPAS) measurements corresponded to the time course of increasing cutaneous pain tolerance latency assessed by dolorimetry.

Pain self-reports following intrathecal morphine infusion (2.25 or 1 mg) followed a similar though slower onset to that reported by patients receiving intravenous morphine and was of lesser degree. In contrast, heat beam dolorimetric evidence of increased cutaneous pain tolerance (which was of lesser degree than following i.v. morphine) did not reach its maximum during the 4 h measuring period. A dissociation was noted therefore between the self-reported relief of endogenous pain and dolorimetrically measured cutaneous analgesia following intrathecal morphine administration. Linear regression correlation analysis characterized this phenomenon as a positive correlation between cutaneous pain tolerance and pain relief self-report following intravenous morphine infusion and a negative correlation following intrathecal administration.

We propose that the phenomenon may be due to intrathecal morphine acting via two separate compartments: one spinal and one supraspinal. We further propose that the prolonged segmental action of intrathecal morphine is continued through supraspinal processes, which induce dolorimetrically measurable elevation of pain tolerance level.

Key words: Dolorimetry; Analgesia; Intrathecal; Intravenous; Morphine; Chronic pain

Introduction

Assessment of response to analgesic therapy is vital to the rational choice of an analgesic agent, its dose and route and in the continuing assessment of chronic analgesic effect. The development of tolerance to opiate drugs is probably inevitable, but it behooves the clinician scientist to estimate, in as objective a fashion as possible, the differential extent to which the pain patient's increased drug demand is due to increasing severity of the dependence condition, to increasing pain or to diminishing analgesic effect. The assessment must be made in the knowledge that pain of pathologi-

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cal origin is never constant in intensity, though it may be qualitatively unremitting. Such rational evaluation of analgesic intensity has been the subject of considerable investigation using a variety of instruments for its quantification. Fundamentally, these studies are of two types: (1) those which attempt to assess, in pain patients, the subjective relief of pathological pain engendered by analgesics [6]; and (2) those which attempt the quantification of analgesic efficacy in relieving an applied, experimental, pain in normal subjects [10]. Both studies are useful, but there can be no question that pain investigators do not presume *a priori* equivalency between these two states. Indeed, it has recently been found by Lipman et al. [8] that the perception of an incident, applied, pain is significantly influenced by the existence of an underlying pathological pain, in chronic pain patients. This does not necessarily render the phenomenon of analgesic effect unaccessible to objective study in pain patients, however.

In the development of relevant model algesic stimuli for application to patients and normal volunteers for the assessment of a drug's analgesic effects (see (2) above), it necessarily follows that analgesic drugs which are known to relieve clinical pathological pain must also attenuate the perceived pain of the experimental algesic stimulus. If it does not (as in the case of the heat beam dolorimetric pain *threshold* measures of Chapman and Feather [2]), then the relevancy of studies using such an algesic stimulus and their relationship to endogenous pain is called into question. Our previous finding that cutaneous thermal pain *tolerance* measures are subject to modification by coexistent endogenous pathological pain states [8] have led us to propose the cutaneous thermal pain tolerance as a relevant measure by these criteria.

The present study was undertaken to compare and contrast the subjective analgesic effects of morphine on pathological pain, as assessed by self-rating scales — with the objective evidence of morphine's analgesic effect on cutaneous pain tolerance levels assessed by the heat beam dolorimeter. Evaluations were conducted before and after morphine was administered intravenously (5 patients) or intrathecally (5 patients).

Methods

Subject demographics

Twenty-four normal volunteers were recruited from among the investigators, their colleagues and students. Eight were male and sixteen were female, with a mean age of 31 ± 9 years (range 19–55). Those patients ($n = 5$) assigned to the intravenous morphine study were males (aged 59, 62, 65, 66 and 72 , years) suffering chronic arachnoiditis complicated by varied surgical histories. Patients ($n = 5$) assigned to the intrathecal morphine study suffered the pain of metastatic cancer, four were male and one was female (aged 30, 48, 60, 72 and 38, respectively). Informed consent pursuant to Institutional Review Board approval was obtained from all subjects.

Intravenous morphine infusion test

Five chronic pain patients were admitted to intensive care monitoring and fitted with an intravenous butterfly catheter in the left antecubital fossa through which 0.9% saline was delivered at a constant flow rate of 100 ml/h. Opiate medications were withdrawn 24 h prior to the test. Baseline pain self-reports and heat beam dolorimetry (HBD) estimates were obtained usually at 08.00 h on the day of the test, following which morphine sulfate solution (1 mg/ml) was administered as six 5.0 mg doses at 5 min intervals to a total dose of 30 mg. Subjective pain estimates (pain self-reports — see below) were obtained every 30 min for 6 h, and HBD evaluations obtained hourly.

Intrathecal morphine test

Selected chronic pain patients ($n = 5$) had previously been tested and found to experience significant relief of their chronic pain in response to intrathecal preservative-free morphine (1 mg/ml) administered via chronic indwelling intrathecal lumbar catheter. Patients were initially permitted to vary their dosing level to a stable demand such that the investigators and patients together were able to select a single dose that would obtain 18–24 h of pain relief prior to this investigation. At the time of the intrathecal morphine test, the pain of each patient was controlled by 1 injection

per day of the following doses: patient LH = 2.25 mg; CH = 1 mg; WM = 1 mg; WL = 1 mg; BL = 1 mg. On the day prior to the test, patients were admitted to the Clinical Research Center and all medications withheld, pain self-reports were completed hourly whilst awake. At 08.00 h (± 1 h) on the day of test, baseline HBD and self-report evaluations were conducted and the requisite dose of morphine administered. Pain self-reports were completed at 30 min intervals and HBD evaluations conducted at 15 min and each hour thereafter.

Pain self-reports

Two visual analogs and two category scales were administered to the patients on a single page questionnaire at the intervals specified by the study. This questionnaire presented a 10 cm visual pain analog scale (VPAS, with limits of no pain–maximum possible pain) and two category choice boxes: pain severity (none, a little, some, a lot, terrible) and pain relief (none, a little, some, a lot, complete). The analog scale was a straight 10 cm line, unrelieved by index marks, which the patient marks in the usual way. This was later scored by measuring the distance from 0 cm (no pain). All patients were presented pain self-report questionnaires in standardized fashion, given identical instruction and were not permitted to review their prior responses. Only visual pain analog scale data are reviewed in this report.

Heat beam dolorimetry

Heat beam dolorimetry for evaluation of pain tolerance was conducted according to the method of Lipman et al. [8] except that the dolorimeter was adjusted to deliver a relatively low thermal stimulus intensity, independently calibrated by calorimetry at 15.33 $mW \cdot cm^{-2} \cdot sec^{-1}$. The method was otherwise as described above, bilaterally evaluating cutaneous pain tolerance levels at loci encompassing C_6/T_1, C_7/C_8, T_3 and L_5 dermatomes. More specific dermatomal assignment is not practical due to the normal physiological overlap between sensory radicular autonomous zones. The C_6/T_1 site on the volar forearm is more distal than the C_7/T_1 site referred to in the publication above by Lipman et al. [8]. Briefly, a thin layer of matte black paint is applied to the cutaneous target sites and when dry is subjected to the constant thermal stimulus, which the patient feels first as warmth, then heat and eventually as pain. The patient is carefully instructed not to respond by movement until the pain is 'intolerable.' Movement or activation of a remote contact disengages the beam via a photocell mechanism and reports the latency to response in hundredths of a second. Measurements are recorded from stimulus applications presented to each site in turn at least 4 times in any one evaluation at intervals of approximately 2 min.

Statistics

Analysis of variance (ANOVA) was conducted on normalized heat beam tolerance latency (transformed as %Δ from control). Correlations of Δ% HBD tolerance latency with Δ% in subjective pain relief (Δ% VPAS) were computed by multiple linear regression analysis (least squares method).

Results

Normative pain tolerance data from the 24 control subjects are shown in Table I, together with the baseline (predrug) value for pain patients. The mean latency value obtained with 15.33 $mW \cdot cm^{-2} \cdot sec^{-1}$ was longer than that obtained previously using a stimulus intensity of 75 $mW \cdot cm^{-2} \cdot sec^{-1}$ [8]. Thus, the normal heat beam tolerance latency is stimulus intensity-dependent. Normative data show an asymmetry which is greatest at the C_7/C_8 site ($P < 0.0001$, Student's paired t test). Our studies to date indicate that the phenomenon is not related to handedness [Lipman, Blumenkopf and Lawrence, in prep.]. With the exception of patients WM and LH who evinced clear signs of the opiate withdrawal syndrome at the time of baseline testing, the general trend is toward elevated baseline tolerance latencies in the pain patients compared with controls.

Morphine administration was not accompanied by complications in any of the procedures described. To eliminate the biasing effect which might result from differing baseline tolerance values, the bilateral average percent change in HBD

TABLE I

BASELINE PAIN TOLERANCE LEVELS IN NORMAL VOLUNTEERS (n = 24) AND PAIN PATIENTS (n = 10) IDENTIFIED BY CODE (Pt ID) BEFORE DRUG ADMINISTRATION

Stimulus intensity 15.33 $mW \cdot cm^{-2} \cdot sec^{-1}$.

Test site	Volunteers' data (n = 24) (group mean ± S.E.M., sec)	Patient ID									
		Intravenous					Intrathecal				
		SW	CL	HN	WS	WL	WM *	WL2	BL	CH	LH *
C_6/T_1L	5.96 ± 0.29	16.65 ± 0.32	7.09 ± 0.86	–	–	7.28 ± 0.69	–	8.19 ± 0.90	6.77 ± 0.54	7.69 ± 0.26	3.54 ± 0.21
C_6/T_1R	6.09 ± 0.25	16.34 ± 1.85	8.23 ± 0.25	7.77 ± 0.48	7.62 ± 1.60	8.57 ± 0.82	–	7.42 ± 0.55	6.92 ± 0.29	5.80 ± 0.34	3.76 ± 0.47
C_7/C_8L	6.00 ± 0.27	16.51 ± 0.58	7.00 ± 0.86	–	7.36 ± 0.73	–	4.23 ± 0.17	8.46 ± 0.90	8.11 ± 0.89	7.83 ± 0.44	4.40 ± 0.18
C_7/C_8R	7.48 ± 0.29	15.54 ± 1.40	11.05 ± 0.16	11.41 ± 0.31	9.64 ± 1.13	–	5.81 ± 0.47	8.44 ± 0.63	12.01 ± 1.26	11.00 ± 1.30	3.88 ± 0.32
T_3L	5.57 ± 0.29	14.30 ± 2.40	8.08 ± 1.19	7.34 ± 0.84	7.38 ± 1.59	6.63 ± 0.62	–	7.31 ± 0.84	7.29 ± 1.06	6.06 ± 0.19	2.58 ± 0.51
T_3R	5.30 ± 0.28	11.10 ± 0.07	8.57 ± 0.60	5.64 ± 0.51	6.10 ± 0.30	5.62 ± 0.46	–	7.62 ± 1.22	6.31 ± 0.38	5.15 ± 0.45	2.31 ± 0.29
L_5L	7.35 ± 0.31	18.50 ± 1.10	8.58 ± 0.59	8.93 ± 0.54	7.59 ± 1.07	7.47 ± 0.47	–	8.43 ± 0.64	8.51 ± 0.76	6.81 ± 0.55	4.57 ± 0.41
L_5R	7.25 ± 0.33	15.90 ± 1.20	13.43 ± 1.04	8.83 ± 0.70	8.02 ± 1.01	8.18 ± 0.60	–	7.36 ± 0.58	9.42 ± 0.43	5.68 ± 0.60	4.36 ± 0.74

* Opiate withdrawal signs present at time of test; –, missing data.

tolerance latencies was calculated for each patient at each time interval and the global average computed for the group. Fig. 1 illustrates these average findings for both i.v. and i.t. groups. Also shown in the figure is the normalized subjective pain relief measure (ΔVPAS) which is calculated as a ratio of the control (pre-drug) VPAS value to the VPAS value at each time interval. Values of VPAS > 1.0 represent subjective pain relief, therefore, as reported by the patient.

As can be seen in the figure, both i.v. and i.t. treatments engendered self-reported relief of endogenous pain, a lesser overall average in the degree of analgesia being reported by those administered i.t. morphine compared with i.v. morphine. This difference was at the borderline of significance ($P = 0.05$, ANOVA), at the 2 h time interval. HBD tolerance latency responses likewise increased following both analgesic treatments, and the HBD measure illustrates its increase over time at each bilateral site following treatment. Group average % HBD latencies had large standard errors since this figure compounds both interlateral and interindividual differences. The mean response of the group's average was nevertheless toward an increase — indicative of increasing tolerance to exogenous pain. The increase was quantitatively greater, initially, at all sites following i.v. than i.t. morphine, yet this difference was not significant ($P > 0.05$) except at the peak time of i.v. analgesia which differed for each site. This peak time was between 2 and 3 h at C_6T_1 ($P < 0.05$), 2–3 h at T_3 ($P < 0.05$), and at 1 h at C_7C_8 ($P < 0.05$). The peak response to i.v. morphine was much limited at L_5 and occurred at approximately 1 h, plateauing thereafter. Only at the level of injection, at L_5, did the group average Δ% HBD tolerance latency of i.t. patients exceed the effect engendered by i.v. treatment. At this site, the value obtained following i.t. treatment continued to increase with time, becoming significantly greater than the i.v. effect ($P < 0.05$) after the latter had diminished 4 h after injection.

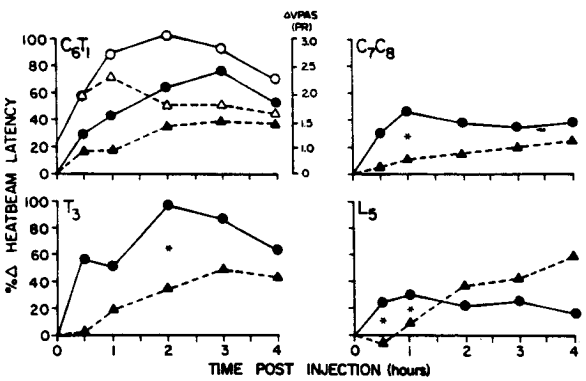

Fig. 1. Mean HBD tolerance latencies (% change from control of patients administered either intrathecal (n = 5, i.t., ▲----▲) or intravenous (n = 5, i.v., ●———●) morphine sulfate (see text for dose). Left–right averages are shown for approximate dermatomal locations C_6/T_1, C_7/C_8, T_3 and L_5. The average subjective pain relief scores (Δ VPAS) for these two groups of patients are shown at top left (i.t., Δ----Δ; i.v., ○———○) ($P < 0.05$, * ANOVA).

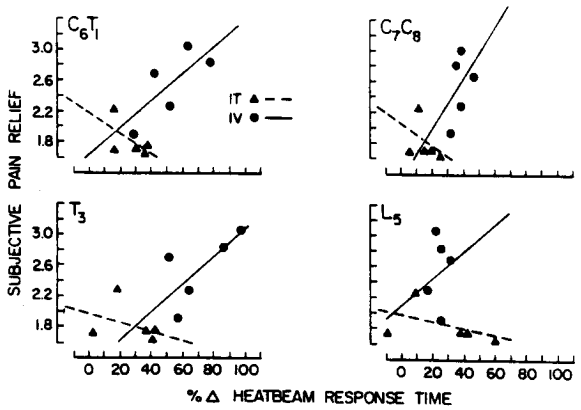

Fig. 2. Least square linear regression correlation analysis between subjective pain relief (Δ VPAS) and Δ% HBD tolerance latency for patients administered i.t. (▲----▲) and i.v. (●———●) morphine.

The correspondence between subjective (VPAS) and 'objective' (Δ% HBD latency) indices of endogenous and exogenous pain relief was compared by multiple linear regression. Fig. 2 illustrates these data. The increase in HBD latency to i.v. morphine was positively correlated with subjective relief at all sites, though this did not reach the level of significance due to the small value of N (C_6T_1, $r = 0.88$, $P = 0.12$; C_7C_8, $r = 0.441$, $P = 0.45$; T_3, $r = 0.78$, $P = 0.12$; L_5, $r = 0.22$, $P = 0.719$).

In contrast, the increase in HBD latency to i.t. morphine was negatively correlated with subjective pain relief (C_6T_1, $r = -0.58$, $P = 0.29$; C_7C_8, $r = -0.35$, $P = 0.48$; T_3, $r = -0.35$, $P = 0.56$; L_5, $r = -0.49$, $P = 0.40$).

Discussion

Thermal cutaneous dolorimetry was first carried out by Wolff et al. [13], using themselves as normal volunteers. These authors demonstrated their pain thresholds – the lowest thermal stimulus that produces noticeable pain (in their hands, applied for 3 sec) — are elevated by opioids including morphine, dihydromorphinone, methyldihydromorphinone and codeine in a dose-dependent manner. Christensen and Gross [3] extended these findings to meperidine and methadone, and Andrews [1] showed that the same phenomenon occurs when morphine is administered to morphine addicts on a daily schedule of administration. Tolerance to the pain threshold elevating effect was found to occur on repeated administration in these addicts. Notwithstanding this early work on the pain threshold's sensitivity to analgesics, these tests require careful and thorough training of the volunteer subject (Gross et al. [5] trained their normal volunteers for 10 days prior to the study) to recognize the pain threshold and show major inter-individual variation to morphine's analgesic effect, even with careful selection and training of test subject [7]. The method suffers from major disadvantages when transferred to the clinical situation where the test subject, who may suffer excruciating pain of endogenous pathologic origin, is less able to attend to the minor sensory nuances of the pain threshold. Eriksson et al. [4] report that, in pain patients who experienced significant analgesia from epidural morphine, there was no detectable change in the cutaneous thermal pain threshold.

In contrast to the foregoing, the present study used the pain tolerance limit as its end point. The pain tolerance level exhibits linear change with stimulus intensity and yet it shares a sufficient commonality with the physiological processes of endogenous pathological pain perception that is positively influenced by changes in the endogenous pain state [8].

Although the 'normal volunteer group' is by no means representative of the global normative universe, being generally younger, and of course healthier, than the patient groups, we believe that the use of this group as a reference sample is valid, differing from the patients largely by their lack of pain. Within this normal group, no overall age or sex dependency has been found to HBD tolerance latency at any stimulus intensity [Lipman, Lawrence and Blumenkopf, in prep.].

The present study, conducted in a small number of patients, tends to confirm the 'pain tolerance level,' at the stimulus intensity we have used, as a useful algesic stimulus for objective analgesic evaluation in pain patients.

Our general findings are: firstly, that the HBD procedure detects the cutaneous analgesic effects of both i.v. and i.t. morphine, secondly that the time courses of subjective and objective measures of analgesia are similar, within the error of the method, and thirdly that the correlations between subjective and objective measures differ following treatment by the two different routes. Positive correlation, as found following i.v. administration, suggests that the rates of change of each of the two measures parallel each other. Negative correlation, as found following i.t. administration, suggests that they do not. Fig. 1 reveals how this occurs: HBD tolerance latencies of i.t. morphine-treated patients continue to rise throughout the 4 h measurement interval — in contrast to i.v.-treated patients — during the time of increasing and then decreasing subjective relief of endogenous pain.

It is notable that patient LH received more than twice the dose (2.25 mg) of morphine than did the other members of the group (1 mg), yet did not experience a greatly different increase in pain tolerance latency. We cannot ignore the possibility that the different types of clinical pain experienced by the different patients could influence the time course and intensity of morphine's analgesic effect, nor can we ignore the fact that each patient was undoubtedly experiencing different degrees of endogenous pathological pain which interfered with their analgesic response in this test and with their baseline pain tolerance latencies. Indeed our data support such a hypothesis (Table I) [8]. It would nevertheless be interesting to speculate that the similarity of dolorimetric response under different morphine doses arises because patients are differentially tolerant to intrathecal morphine. This hypothesis is amenable

to testing, and we continue to test these patients at intervals of time to investigate the development of tolerance to the analgesic effect of daily intrathecal morphine administered for control of their pathological pain.

It is interesting to speculate on the hyperalgesic baseline tolerance latencies of patients WM and LH, both of whom evinced mild opiate withdrawal syndromes. The phenomenon of withdrawal irritability or hyperesthesia is well known [12], but the present study suggests that the phenomenon is associated with a genuine, objective increase in cutaneous pain sensitivity (reduced tolerance) or to an increased or heightened perception of the aversiveness of the sensation.

Our findings with regard to the time courses of subjective and objective effects of these two methods of morphine administration are intriguing. The HBD tolerance profile reveals a progressively increasing effect of i.t. morphine following a minimal effect ($P > 0.05$) within the first hour at all sites. Measurements made at the dorsum of the feet, at the L_5 dermatome adjacent to the intrathecal injection site, reveal no greater initial elevation of tolerance than at higher, more rostral, dermatomes. This tends to rule out a selective segmental action for the i.t. morphine effect on cutaneous pain tolerance. Clearly, no delay occurred in the immediate subjective effects of this treatment compared with the i.v. route. We cannot exclude the possibility that the early subjective effect of i.t. morphine on endogenous pain is placebo-mediated [9], and such a study would involve questionable ethical problems in the present patient population. Our data suggest that by the 4th h after injection this endogenous pain relief is mediated at rostral sites in the neuraxis to which morphine must flow from the i.t. depot.

This time course profiles of i.v. morphine, with high positive correlation between subjective and objective effects, indicate that these two phenomena co-vary; that is, that the (presumably central) substrates of these two effects are the same or are affected at the same rate — in marked contrast to i.t. morphine's effect.

In conclusion, therefore, these preliminary findings suggest that intrathecal morphine exerts analgesic effects via a supraspinal mechanism in common with the effects of the intravenous route. The present conclusion that subjective effects of i.t. morphine on endogenous pain precede local segmental effects on cutaneous pain tolerance awaits confirmation by placebo-controlled studies. The pain tolerance method of cutaneous heat beam dolorimetry does appear adequate to the task of determining this mechanism, however.

Acknowledgements

The clinical assistance of Brigitte Lanford, Deborah L. White and Stephen Tolchard is gratefully acknowledged, as is the expert computing assistance of Patricia L. Lawrence.

This study was conducted using the facilities of the Clinical Research Center of Vanderbilt University (Project No. 357; Chief Investigator, Dr. Lipman).

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