Br J clin Pharmac 1994; **37**: 325–333

A comparison of the antinociceptive effects of imipramine, tramadol and anpirtoline

T. HUMMEL[1], C. HUMMEL[2], I. FRIEDEL[1], E. PAULI[2] & G. KOBAL[1]
[1]Department of Experimental and Clinical Pharmacology and Toxicology, University of Erlangen-Nürnberg, Universitätsstrasse 22, 91054 Erlangen, and [2]Department of Neurology, University of Erlangen-Nürnberg, Schwabachanlage 6, 90154 Erlangen, Germany

1 The pain relieving properties of imipramine (100 mg orally), tramadol (150 mg orally), and anpirtoline (60 mg orally) were compared in 16 healthy subjects in a cross-over, double-blind, randomized, and placebo-controlled study. Anpirtoline exhibits analgesia which is possibly mediated via serotoninergic pathways, whereas tramadol exerts its effects at opioid receptors. The pain-relieving effect of the tricyclic antidepressant imipramine may involve both serotoninergic and opioid mechanisms.

2 Chemo-somatosensory event-related potentials (CSSERP) were recorded after painful stimulation of the nasal mucosa with carbon dioxide. Subjects rated the perceived intensity of the stimuli by means of a visual analogue scale. In addition, acoustically evoked responses were recorded, the spontaneous EEG was analyzed in the frequency domain, the subjects' vigilance was assessed in a tracking task, and side effects of the drugs were monitored.

3 Anpirtoline and tramadol produced a decrease of both CSSERP amplitudes and subjective estimates of pain, the effects of the former compound being greater. In contrast, after administration of imipramine no change of CSSERP amplitudes could be detected, whereas the subjective estimate of pain intensity decreased significantly. This was accompanied by a significant decrease of arousal indicating that pain relief produced by acute administration of imipramine was primarily related to its sedation action.

4 The analgesic properties of anpirtoline were demonstrated in man. Tramadol was characterized as a weak opioid analgesic. In contrast, imipramine appeared to produce its pain-relieving effects predominantly by non-specific actions. It is hypothesized that different analgesics may change ERP sources in a drug-specific manner.

Keywords anpirtoline tramadol imipramine event-related potential EEG pain nociception analgesia chemical stimulation trigeminal nerve

Introduction

Anpirtoline is a novel 5-HT_1 receptor agonist with antidepressant/antinociceptive-like effects [1, 2]. Its affinity for 5-HT_{1B} receptors in rat brain is approximately five times as high as that for 5-HT_{1A} receptors [2]. Anpirtoline reversed isolation-induced impairments in mice (social behaviour deficit test). In addition, it increased the swimming time in the forced swimming test similarly to imipramine and desipramine. In the 'electrostimulated pain test' anpirtoline increased the pain threshold in a dose-dependent manner an effect which was abolished by pretreatment with cyproheptadine or propranolol [2]. Engel *et al.* [3] showed that anpirtoline exhibits non-significant affinities for mu, delta and kappa opioid receptors. It was effective in the tooth pulp stimulation test in dogs, the mouse hot plate and the mouse

Correspondence: Dr Thomas Hummel, Department of Experimental and Clinical Pharmacology and Toxicology, University of Erlangen-Nürnberg, Universitätsstrasse 22, 91054 Erlangen, Germany

'electrostimulated pain test'. Its analgesic effects were not blocked by naloxone [3]. Anpirtoline was not self-administered by codeine-dependent rhesus monkeys. It did not produce weight loss upon withdrawal after chronic administration in rats [3]. Swedberg *et al.* [4] reported that the effects of anpirtoline could not be substituted by the opioid agonists codeine, pentazocine, and tramadol, and they were not antagonized by the opioid antagonist naltrexone. Engel *et al.* [3] also showed that anpirtoline produced no antipyretic or anti-inflammatory effects in rats.

Thus, anpirtoline appears to possess a strong analgesic action which may be mediated via 5-HT_1 receptors in the central nervous system [5–8]. To investigate its potential analgesic action in man we have used a technique involving measurement of chemo-somatosensory event-related potentials (CSSERP) after painful stimulation of the nasal mucosa with carbon dioxide [9]. These chemical stimuli are considered to be natural, specific stimuli for the excitation of the trigeminal nociceptive system [10–13]. The late nearfield event-related potentials [14] elicited in the EEG are highly correlated with subjective pain ratings [15]. Moreover, one of the sources of these responses has been localized in the somatosensory area SII [16] which is assumed to be a primary projection area for nociceptive afferents [17]. This model has been employed successfully to measure the action of various analgesics [18–20].

As control drugs we have used tramadol and imipramine. Compared with other opioids tramadol is considered to be a weak analgesic suitable for the treatment of acute and chronic pain [21–25]. Its major advantages appear to be a low risk of respiratory depression [26] and a low risk of dependence [27, 28]. In contrast, the tricyclic antidepressant imipramine is primarily used in chronic pain states [29–31], although there are studies indicating the efficacy of tricyclics in acute experimental pain [32, 33]. The analgesic properties of tricyclics are believed to arise from blockade of catecholamine reuptake and activation of the opioid system [33–36].

The three drugs were also compared with respect to vigilance and arousal (frequency analysis of spontaneous EEG, acoustic event-related potentials). Thus, it was hoped to discriminate non-specific effects from the nociceptive actions of the drugs.

Methods

Sixteen healthy subjects (eight male, eight female, 21–36 years of age) participated in the study after they had provided written informed consent. The Ethics Committee of the University of Erlangen-Nürnberg approved the study, which was performed in accordance with the Declaration of Helsinki/Hong Kong.

Study design

A double-blind, randomized, controlled, four fold cross-over study design was chosen. Prior to a standard breakfast taken immediately before the beginning of each experiment the subjects fasted for 8 h. Each experiment consisted of two testing sessions one of which took place before administration of the medication and the second 140 min thereafter. This protocol was used because peak plasma concentrations of all three drugs are reported to occur at about 2 h after administration [37–39]. The drugs were given orally together with 200 ml water (placebo, 60 mg anpirtoline, 150 mg tramadol, and 100 mg imipramine in identical brown capsules). Each session lasted for approximately 30 min. During this time, 32 painful carbon dioxide stimuli at two concentrations were applied to the subject's nasal mucosa.

In an additional training session prior to the actual experiments subjects were acquainted with the experimental procedures, and, specifically, with a breathing technique (velopharyngeal closure [15]), whereby respiratory flow inside the nasal cavity during stimulation is avoided. During this session they were also trained to perform both the tracking task and the estimates of pain intensity.

During the experiments the subjects were seated comfortably in an air-conditioned room with convenient temperature. White noise of approximately 50 dB SPL was used to mask the switching clicks of the stimulator.

Painful stimulation of the nasal mucosa

The painful carbon dioxide stimulus was applied under conditions that did not simultaneously activate mechano- or thermosensors in the nasal mucosa (for further details see [9, 19]). The stimulus duration was 250 ms, and intervals between stimuli varied randomly between 40 and 50 s. Painful stimulation with two CO_2 concentrations (55 and 66% v/v) was applied to the left nostril in a randomized sequence. Since it was demonstrated previously that stimulation using concentrations well above threshold produced more reliable results [19, 20, 40], only responses to the stronger stimuli were subjected to statistical analysis.

Estimates of pain intensity

After application of each painful stimulus, the subjects estimated the perceived pain intensity in relation to a standard stimulus (66% v/v CO_2) which had been applied at the beginning of the first session. The intensity of this standard was defined as 100 estimation units (EU). The pain intensity was rated using a visual analogue scale [41] displayed on a computer monitor. The length of a red bar representing the intensity of the actual stimulus was adjusted by means of a joystick in relation to the length of a fixed blue bar representing the intensity of the standard stimulus. If the actually perceived intensity was less than the intensity of the standard, the subjects reduced the length of the red bar accordingly. In case no pain was perceived, subjects were instructed to let the red bar disappear (0 EU). In case the actual stimulus was perceived as stronger than the standard stimulus the red bar was increased in comparison with the blue bar. All estimates obtained during one session were averaged for statistical evaluation.

Pain-related chemo-somatosensory event-related potentials (CSSERP)

The EEG was recorded from 4 positions (F3, F4, P3, and P4) of the 10/20 system referenced to linked earlobes (A1 + A2). Blink artifacts were monitored from an additional site (Fp2/A1 + A2). The sampling frequency of the stimulus linked EEG-segments of 2048 ms was 250 Hz (bandpass 0.2 to 30 Hz; pre-stimulus period 500 ms). After analogue-to-digital conversion (CED 1401, Cambridge Electronic Devices, UK), the EEG-segments were stored on an IBM compatible computer. These data were evaluated off-line using an averaging technique which yielded late nearfield event-related potentials (for review see [14]). All single responses contaminated by eye blinks or eye movements were discarded from the average, and average responses with a blink artifact larger than 40 μV in the Fp2-lead were excluded from further analyses. The latencies T-N1, and T-P2 of the CSSERP were measured in relation to stimulus onset. In addition, the peak-to-peak amplitude N1P2 was evaluated [20].

Acoustic event-related potentials (AERP)

Twenty acoustic stimuli (1 kHz bursts, 55 dB HL, duration 100 ms; Zeissberg, FRG) were applied randomly to the right ear during intervals between painful stimulation. The analysis of event-related EEG segments was performed as described for the CSSERP.

Spontaneous EEG

To determine background EEG activity just prior to the onset of painful stimulation, pre-stimulus EEG segments of 4096 ms were recorded (sampling frequency 125 Hz). After examination for eye blinks and artifacts produced by muscle activity, the segments were submitted to frequency analysis (Fast Fourier Transformation). The resulting power spectra were averaged. The integrated power of the 6 frequency bands delta (0.9–3.4 Hz), theta (3.6–7.0 Hz), $alpha_1$ (7.3–10.0 Hz), $alpha_2$ (10.2–12.9 Hz), $beta_1$ (13.1–18.0 Hz), and $beta_2$ (18.3–20.9 Hz) was used for further statistical evaluation [20].

Tracking performance

To detect changes in vigilance and/or motor coordination, the subjects were requested to perform a tracking task on a video screen [19]. They had to keep a small square, which could be controlled by a joystick, inside a larger one, which moved around unpredictably. Performance was measured by counting how often and for how long the subjects lost track of the randomly moving square. The data were averaged for each session.

Cardiovascular parameters

Both systolic and diastolic blood pressure (Riva-Rocchi) were recorded in the sitting subjects before and after administration of the drugs, prior to the second session of the experiment.

Adverse reactions

After the second session (i.e., 170 min after drug intake) the subjects were asked to report all subjective effects of the medication. Their reports were recorded verbatim and categorized off-line under headings such as 'elation in mood' according to the WHO Adverse Reaction Terminology [42]. In addition, the subjects were requested to estimate the degree of four selected adverse reactions using visual analogue scales ('tiredness', 'drowsiness', 'vertigo', and 'sickness') where the left hand score (0) was defined as 'no such symptom' and the right hand score (100) was 'symptom experienced at maximum'.

Statistical analysis

The differences between data obtained after and before administration of the drugs were calculated and subjected to analysis of variance (1-way ANOVA, repeated measurement design, with 'drug' as the within-subject factor). In the case of the electroencephalographic measures (CSSERP, AERP, frequency analyses of spontaneous EEG) 2-way ANOVAs were performed (within-subject factors 'drug' and 'recording position') separately for the two frontal, and the two parietal recording sites. Differences between the effects of placebo and drug were assessed by *t*-tests when the ANOVA yielded significant results ($P < 0.05$). In these cases, 95% confidence intervals (CI) were also computed.

Results

Means and standard deviations of the measured variables are shown in Table 1. One subject dropped out of the study because of side effects (hyperventilation, nausea, drowsiness, hypotension) after administration of imipramine which lasted for approximately 30 min. However, since these effects began 5 min after drug intake they may not have been drug-related.

To illustrate the shape of the CSSERP response and changes in relation to administration of the drugs, Figure 1 shows responses in a representative subject.

Pain intensity estimates

Estimates of the intensity of pain decreased after administration of imipramine, tramadol, and anpirtoline but increased after placebo (Figure 2). Thus, analysis of variance revealed a significant effect (factor 'drug', $F = 2.90$, $P < 0.05$) for anpirtoline ($P < 0.05$) and imipramine ($P < 0.05$) but not for tramadol ($P < 0.1$) (95% CI: placebo −6.49 to 16.54; anpirtoline −19.53 to −5.19; tramadol −19.59 to 2.82; imipramine −21.89 to 0.58).

Table 1 Means and standard deviations (s.d.) of chemo-somatosensory event-related potentials, acoustic event-related potentials, and the frequency analyses of the spontaneous EEG at all recording positions. The results are represented as differences between data obtained after administration of the medication and baseline measures

		Placebo		*Imipramine*		*Tramadol*		*Anpirtoline*	
		Mean	*s.d.*	*Mean*	*s.d.*	*Mean*	*s.d.*	*Mean*	*s.d.*
Chemo-somatosensory event-related potentials (n = *15*)									
AMPL. N1P2	Pos. F3	1.20	4.31	−0.55	3.10	−3.27	3.37	−3.58	3.95
(μV)	Pos. F4	0.33	3.29	−2.67	4.64	−4.11	6.30	−5.29	5.49
	Pos. P3	−1.74	5.81	−0.66	6.42	−2.97	7.21	−4.62	5.91
	Pos. P4	−2.07	5.52	−0.14	6.19	−2.69	6.05	−4.87	5.34
Lat. N1	Pos. F3	−25	72	1	94	34	107	21	83
(ms)	Pos. F4	−10	57	−3	72	21	96	11	90
	Pos. P3	7	59	18	80	25	98	26	76
	Pos. P4	−7	56	15	89	36	90	26	60
Lat. P2	Pos. F3	2	93	69	103	58	148	34	76
(ms)	Pos. F4	−11	69	46	140	−29	140	39	86
	Pos. P3	32	97	101	163	57	138	2	56
	Pos. P4	2	104	46	165	47	100	11	95
Acoustic event-related potentials (n = *15*)									
Ampl. N1P2	Pos. F3	−3.50	3.94	−6.54	6.29	−1.90	4.08	−4.40	6.18
(μV)	Pos. F4	−3.58	4.70	−6.05	7.41	4.18	4.08	−4.74	5.15
	Pos. P3	−1.28	4.04	−2.50	4.18	−0.53	5.62	−6.80	3.76
	Pos. P4	−2.20	3.72	−1.64	5.55	−1.51	5.36	−4.51	4.68
Lat. N1	Pos. F3	10	22	9	28	−13	32	5	25
(ms)	Pos. F4	8	27	3	37	−7	29	4	23
	Pos. P3	0	18	23	30	−16	29	−7	34
	Pos. P4	−5	20	1	43	−10	30	10	23
Lat. P2	Pos. F3	−16	43	−35	85	−20	72	−17	46
(ms)	Pos. F4	−15	33	−16	67	−30	73	−22	64
	Pos. P3	−20	53	−21	72	−34	54	−22	58
	Pos. P4	−19	76	−50	79	−8	68	−18	56
Frequency analyses of the spontaneous EEG (n = *15; in* $[(\mu V^2\ s^{-1})^{0.5}]$)									
delta-band	Pos. F3	15	31	66	105	1	45	−2	75
	Pos. F4	2	36	48	111	−16	57	−12	49
	Pos. P3	1	36	53	76	6	37	−13	44
	Pos. P4	−12	44	63	81	4	43	−35	53
theta-band	Pos. F3	27	35	55	65	13	30	0	29
	Pos. F4	19	25	57	88	3	37	3	36
	Pos. P3	22	37	37	73	22	25	2	36
	Pos. P4	10	30	53	83	15	32	−20	61
$alpha_1$-band	Pos. F3	23	29	56	64	32	33	13	20
	Pos. F4	22	28	65	95	30	43	10	33
	Pos. P3	32	43	58	65	52	56	22	46
	Pos. P4	7	33	73	82	58	69	14	67
$alpha_2$-band	Pos. F3	11	20	31	27	20	30	7	15
	Pos. F4	10	23	33	46	14	24	3	17
	Pos. P3	11	27	42	50	35	49	8	24
	Pos. P4	14	28	57	57	34	64	−5	45
$beta_1$-band	Pos. F3	13	51	41	57	50	73	3	24
	Pos. F4	17	32	42	69	48	55	1	40
	Pos. P3	13	27	25	46	27	31	16	30
	Pos. P4	7	21	25	45	31	41	−20	97
$beta_2$-band	Pos. F3	1	50	29	49	43	65	−2	15
	Pos. F4	9	25	36	70	41	53	−5	35
	Pos. P3	3	20	16	31	16	22	2	24
	Pos. P4	7	16	13	31	15	32	−12	47

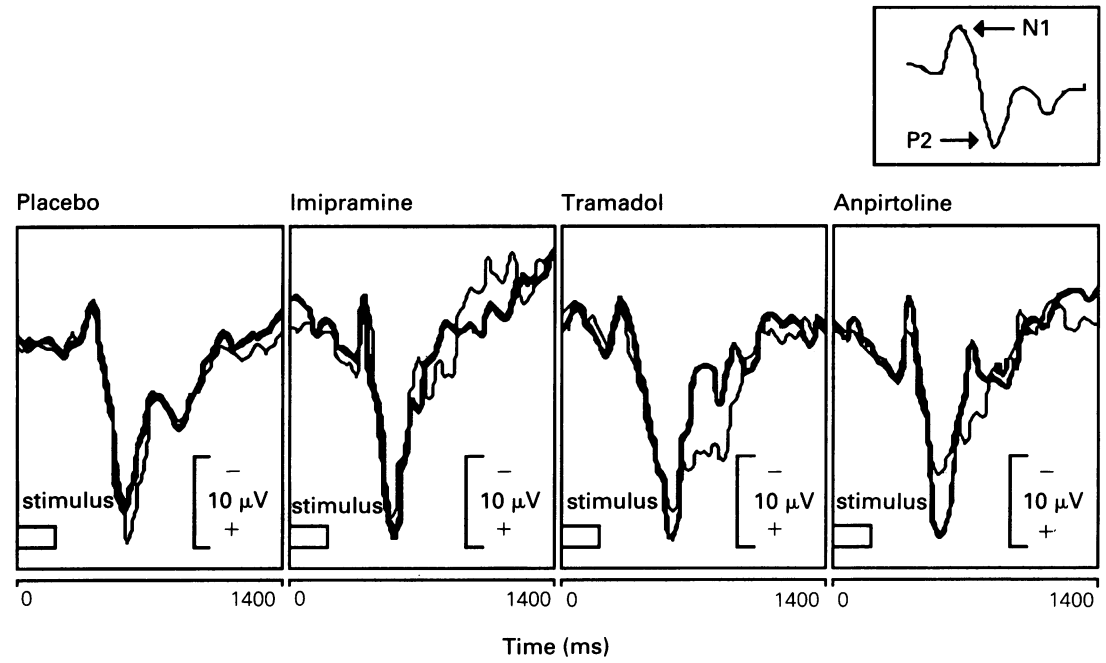

Figure 1 Chemo-somatosensory event-related potentials (CSSERP) at recording position F4 (referenced against A1 + A2) in a representative subject before (bold lines) and 140 min after administration (thin lines) of imipramine, tramadol, and anpirtoline. A schematic drawing of CSSERP peaks N1 and P2 is shown in the inset.

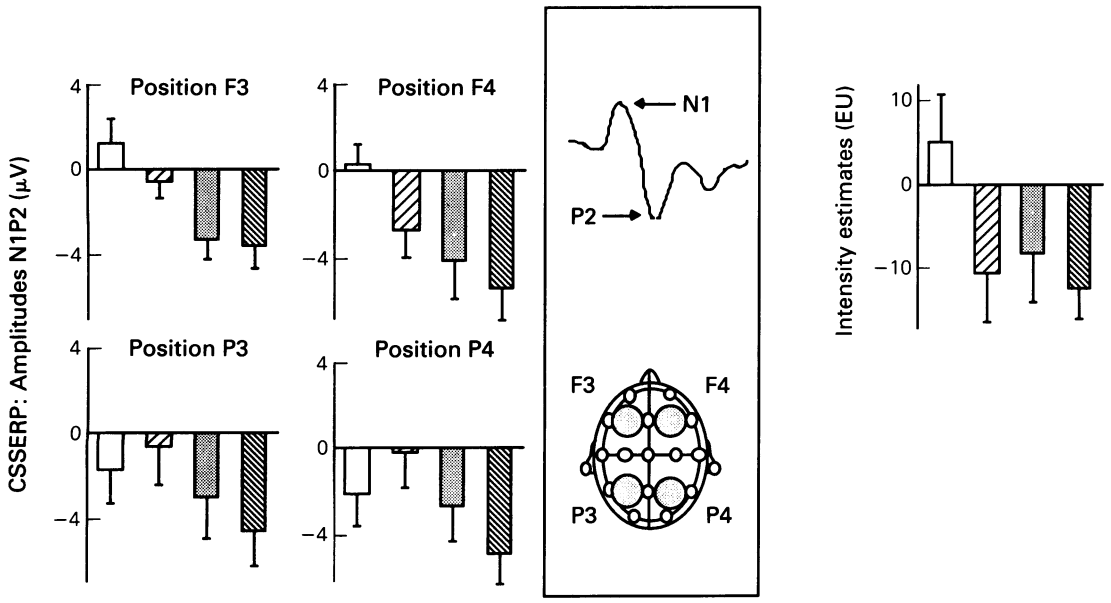

Figure 2 Mean and s.e. mean of the pain-related parameters, intensity estimates and chemo-somatosensory event-related potentials (CSSERP), in relation to baseline measures (differences between measures obtained 140 min after drug administration and baseline). Estimates of pain intensity are expressed as estimation units, i.e., using a visual analogue scale the subjects estimated the perceived pain intensity in relation to a standard stimulus (66% v/v CO_2) the intensity of which was defined as 100 estimation units (EU).
Intensity estimates decreased after administration of all three drugs when compared with placebo. However, a significant decrease of the CSSERP amplitudes was observed only after tramadol and anpirtoline. □ placebo, ▨ imipramine, ▩ tramadol, ▧ anpirtoline.

Chemo-somatosensory event-related potentials (CSSERP)

Anpirtoline caused the largest decrease of CSSERP amplitudes indicating a strong analgesic effect (Figure 2). This was significant ($P < 0.01$) at the frontal but not the parietal recording positions. Administration of tramadol changed the CSSERP in a comparable manner ($P < 0.05$), whereas effects induced by imipramine were similar to placebo (95% CI at position F3: placebo −0.98 to 3.38; anpirtoline −5.58 to −1.58; tramadol −4.98 to −1.56; imipramine −2.12 to 1.02; 95% CI at position F4: placebo −1.34 to 2.0; anpirtoline −8.07 to −2.51; tramadol −7.3 to

−0.92; imipramine −5.02 to −0.32). In contrast to CSSERP amplitudes, statistical analyses of the latencies showed no significant effects of the drugs.

Acoustic event-related potentials (AERP)

Neither amplitudes nor latencies of the acoustic event-related potentials were affected significantly by the drugs.

Frequency analysis of the spontaneous EEG

Analysis of the spontaneous EEG obtained at the frontal and parietal recording positions revealed significant effects ($P < 0.05$) of imipramine for all frequency bands with the exception of the $beta_1$-band, but no significant effects of tramadol and anpirtoline (95% CI delta band: placebo −0.7 to 30.7; imipramine 12.7 to 119.1; 95% CI theta band: placebo 9.3 to 44.7; imipramine 22.1 to 87.9; 95% CI $alpha_1$ band: placebo 8.3 to 37.7; imipramine 23.6 to 88.4; 95% CI $alpha_2$ band: placebo 0.9 to 21.1; imipramine 17.3 to 44.7; 95% CI $beta_2$ band: placebo −24.3 to 26.3; imipramine 4.2 to 53.8).

Tracking performance

The tracking performance increased after placebo and anpirtoline. This indicated, that both drugs did not interfere with the learning process of the typical subject who tends to improve his performance during the course of a single experiment [19, 20]. In contrast, it was significantly worse following administration of imipramine ($P < 0.01$) and tramadol ($P < 0.05$). This decrease of the subjects' performance indicated the presence of sedative drug actions (95% CI: placebo 1.2 to 5.2; anpirtoline 0.0 to 6.4; tramadol −14.7 to 1.7; imipramine −12.9 to −3.5).

Cardiovascular parameters

Neither systolic nor diastolic blood pressure changed significantly after administration of the drugs. Imipramine increased the heart rate ($P < 0.05$) compared with placebo.

Adverse reactions

Imipramine significantly increased 'tiredness' (Figure 3) ($P < 0.01$) (95% CI: placebo −5.06 to 11.7; anpirtoline −9.0 to 23.8; tramadol −7.45 to 21.9; imipramine 15.7 to 39.8). Other symptoms were unchanged by the drugs. Spontaneously reported side effects occurred rarely (Table 2). None of them required medical treatment.

Discussion

The results of the present investigation clearly demonstrated the analgesic properties of anpirtoline. This was indicated by the significant decreases in both subjective rating of the painful stimuli and in

Table 2 Numbers of spontaneously reported adverse reactions

	Placebo	*Imipramine*	*Tramadol*	*Anpirtoline*
Vomiting	0	1	2	1
Debility	0	2	2	0
Trembling inside	0	2	1	0
Dry mouth	0	2	1	2
Blurred vision	0	2	0	1
Flushing	0	1	1	1
Emotional lability	0	1	0	0
Inappropriate elation	0	0	2	0

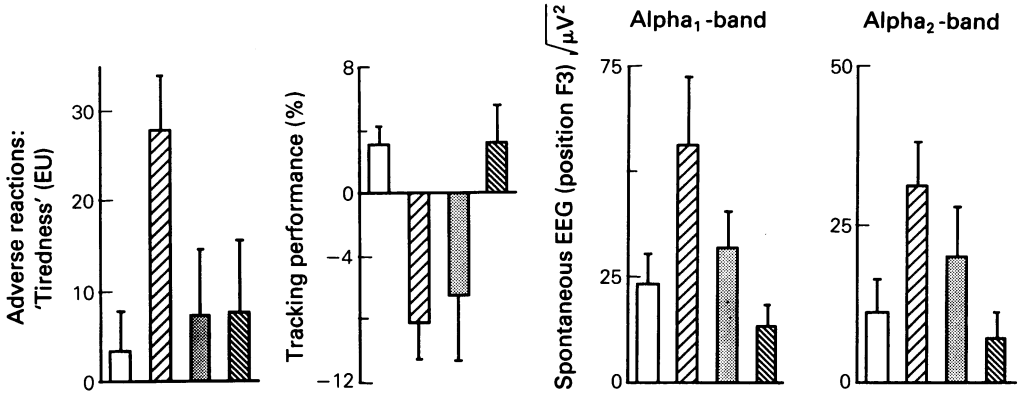

Figure 3 Mean and s.e. mean of parameters related to vigilance (adverse reactions, tracking performance, frequency analyses of the spontaneous EEG) after drug administration. EU = Estimation units. □ placebo, ▨ imipramine, ▩ tramadol, ▧ anpirtoline.

the amplitude of the event-related potentials (ERP). These findings confirm those of Schlicker *et al.* [2] who observed an increase in the nociceptive threshold in experimental animals after administration of anpirtoline. Concerning mean intensity estimates of pain, anpirtoline tended to exhibit a stronger analgesic effect than the opioid tramadol at the doses used. In addition, the mean decrease of CSSERP amplitudes was greatest after anpirtoline.

No significant changes were detected for anpirtoline in the spontaneous EEG nor in the acoustic event-related potentials, indicating the absence of depressant effects which might have contributed to the observed CSSERP changes. Furthermore, performance in the video task actually increased after administration of anpirtoline, indicating the absence of sedative drug actions [19, 20] which is consistent with findings of Swedberg *et al.* [4] in the rat. Anpirtoline was well tolerated by most of the subjects, although vomiting occurred in one subject and two complained of dry mouth.

Tramadol produced only a small decrease in the subjective estimates of pain intensity ($P < 0.01$) but revealed analgesic properties with regard to the decrease of the CSSERP amplitude. Thus, the view that tramadol is a weak opioid analgesic [21, 22, 24, 43, 44] is supported by our data. Other than anpirtoline, tramadol also produced a significant decrease in tracking performance indicating a sedative action. This finding is also supported by the increase of power densities within the alpha-band of the spontaneous EEG [45]. However, there were no significant changes in the ratings of adverse reactions with respect to 'tiredness' or 'drowsiness'. Thus, sedative properties do not appear to be a prominent feature of tramadol [21, 25, 45].

In contrast to tramadol and anpirtoline, imipramine did not change CSSERP amplitudes. However, it did cause a significant decrease in subjective pain rating ($P < 0.05$). This discrepancy may be explained by the non-specific effects of the tricyclic antidepressant. Administration of imipramine resulted in an increase in 'tiredness', a decrease of the tracking performance, and an increase in the power density of the spontaneous EEG, which was most pronounced in the delta- and the alpha-band. Taken together, these results emphasize the sedative properties of the drug [46].

Thus, in terms of anti-nociceptive effects it appears that subjective estimates of pain intensity are less reliable than CSSERP data. As with sleep or distraction [47, 48], the sedative actions of imipramine may lead to pain-relief, but mostly this is not produced by specific anti-nociceptive effects. CSSERP reflect changes in the perception of painful stimuli in a more specific manner [15, 20]. That is, CSSERP reflect certain, limited aspects of the processing of nociceptive information in man and experimental animals [12, 49]. On the other hand, it appears that CSSERP do not reflect pain-relief mediated by unspecific pathways which may have been activated predominantly by imipramine. This specificity of the CSSERP is also supported by preliminary results obtained in 10 subjects [50] which indicate that CSSERP are not susceptible to the sedative effects of diazepam (10 mg orally) or tetrazepam (50 mg orally). In addition, Thürauf *et al.* (unpublished observations in 18 subjects) reported that there was no significant change of CSSERP amplitudes after intravenous administration of 0.065 mg kg^{-1} and 0.13 mg kg^{-1} diazepam. Thus, the present results support the view that the evaluation of both subjective estimates of pain intensities and pain-related ERPs in combination with the monitoring of non-specific drug effects produces a much more complete picture of analgesic effects than the sole analysis of the subjects' responses.

In contrast to the present results, Bromm *et al.* [22] reported that imipramine (100 mg, orally) significantly reduced both subjective pain rating and ERP amplitude in response to electrical stimulation of skin [51]. Although they did not monitor side effects or changes in vigilance, they did analyze the spontaneous EEG. Imipramine was found to produce both a decrease in alpha activity and an increase of theta and delta activity. This may be interpreted in terms of a decreased state of arousal which is in keeping not only with the present results but also with a large body of literature [47]. Therefore, and because electrical stimuli are not ideally suited for the investigation of pain-related ERP in the presence of non-specific drug effects [52–54], the findings of Bromm *et al.* [22] on ERP may have to be reconsidered.

A significant finding of the present study was that analgesic effects of the drugs were only apparent in CSSERP recorded at frontal sites. Previously, Kobal *et al.* [19] observed that both acetylsalicylic acid and the opioid pentazocine produced a significant decrease of the CSSERP at frontal recording positions, while only pentazocine reduced ERP amplitudes at central and parietal sites. From this it may be hypothesized that the cortical generators of the CSSERP [16] are changed by analgesics in a specific manner which alters the topographical distribution of the CSSERP.

In conclusion, we have demonstrated the analgesic properties of anpirtoline, a novel 5-HT_{1A} and $5HT_{1B}$-receptor agonist, in man. Tramadol was characterized as a weak opioid anlagesic. In contrast, imipramine appeared to produce its pain-relieving effects predominantly by non-specific actions which could be characterized by the combined evaluation of pain-related ERP, subjective pain intensity ratings and the monitoring of arousal. It is hypothesized that different analgesics may change ERP sources in a drug-specific manner.

This research was supported by DFG grant Ko812/1-4, the Alexander von Humboldt-Stiftung, Bonn, FRG, and ASTA Pharma AG, Frankfurt, FRG. We thank Dr Richard Traub, University of Iowa, Iowa City, USA, for helpful suggestions during preparation of the manuscript.

References

1 Engel J, Bork A, Nubert I, Schoenberger H. Synthese von 14C-Anpirtolin. *Arch Pharma Weinheim* 1988; **321**: 821–822.

2 Schlicker E, Werner U, Hamon M, Gozlan H, Nickel B, Szelenyi I, Göthert M. Anpirtoline, a novel, highly potent $5HT_{1b}$ receptor agonist with antinociceptive/antidepressant-like actions in rodents. *Br J Pharmac* 1992; **105**: 732–738.

3 Engel J, Scheffler G, Nickel B, Thiemer K, Tibes U, Werner U, Szeleny I. Anpirtoline hydrochloride. *Drugs Future* 1989; **14**: 614–619.

4 Swedberg MDB, Shannon HE, Nickel B, Goldberg SR. D-16949 (anpirtoline): a novel serotonergic (5-HT1B) psychotherapeutic agent assessed by its discriminative effects in the rat. *J Pharmac exp Ther* 1992; **263**: 1015–1022.

5 Zemlan FB, Behbenhani MM, Murphy RM. Serotonin receptor subtypes and the modulation of pain transmission. *Progr Brain Res* 1988; **77**: 349–355.

6 Swaynok J. The role of ascending and descending noradrenergic and serotonergic pathways in opioid and non-opioid antinociception as revealed by lesion studies. *Can J Physiol Pharmac* 1989; **67**: 975–988.

7 Roberts MHT. Involvement of serotonin in nociceptive pathways. *Drug Des Deliv* 1989; **4**: 77–83.

8 Fields HL, Heinricher MM, Mason P. Neurotransmitters in nociceptive modulatory circuits. *Ann Rev Neurosci* 1991; **14**: 210–245.

9 Kobal G. Pain-related electrical potentials of the human mucosa elicited by chemical stimulation. *Pain* 1985; **22**: 151–163.

10 Regan D. *Human brain electrophysiology*. New York: Elsevier, 1989; 280.

11 Steen KH, Reeh PW, Anton F, Handwerker H-O. Protons selectively induce lasting excitation and sensitization to mechanical stimulation of nociceptors in rat skin, in vitro. *J Neurosci* 1992; **12**: 86–95.

12 Thürauf N, Friedel I, Hummel C, Kobal G. The mucosal potential elicited by noxious chemical stimuli: is it a peripheral nociceptive event. *Neurosci Lett* 1991; **128**: 297–300.

13 Anton F, Euchner I, Handwerker H-O. Psychophysical examination of pain induced by defined CO_2 pulses applied to the nasal mucosa. *Pain* 1992; **49**: 53–60.

14 Picton TW, Hillyard SA. Endogenous event-related potentials. In *EEG-Handbook* (revised series, Vol. 3), ed Picton TW, Amsterdam: Elsevier, 1988; 361–426.

15 Kobal G, Hummel T. Brain responses to chemical stimulation of trigeminal nerve in man. In *Chemical Senses, Vol. 2: Irritation*, eds Green BG, Mason JR, Kare MR, New York: Marcel-Dekker, 1989; 123–129.

16 Huttunen J, Kobal G, Kaukoronta E, Hari R. Cortical responses to painful CO_2-stimulation of nasal mucosa: A magnetencephalographic study in man. *Electroenceph clin Neurophysiol* 1986; **64**: 347–349.

17 Chudler EH, Dong WK, Kawakami Y. Tooth pulp evoked potentials in the monkey: Cortical surface and intracortical distribution. *Pain* 1985; **22**: 221–223.

18 Kobal G, Hummel T, Hoesl M. Pain-related electrical evoked potentials by chemical stimuli: Effects of Fentanyl. In *Advances in Pain Research and Therapy* Vol. 12, eds Lipton S, Tunks E, Zoppi M, New York: Raven Press, 1989; 95–98.

19 Kobal G, Hummel C, Nürnberg B, Brune K. Effects of Pentazocine and Acetylsalicylic Acid on Pain-rating, Pain-related Evoked Potentials and Vigilance in Relationship to Pharmacokinetic Parameters. *Agents Actions* 1990; **29**: 342–359.

20 Hummel T, Friedman T, Pauli E, Niebch G, Borbe HO, Kobal G. Dose-related analgesic effects of flupirtine. *Br J clin Pharmac* 1991; **32**: 69–77.

21 Alon E, Schulthess G, Axhausen C, Hossli G. Doppelblindvergleichsstudie über die Wirkung von Tramadol und Buprenorphine auf die postoperativen Schmerzen. *Anaesthesist* 1981; **30**: 623–626.

22 Bromm B, Hermann WM, Scharein, E. Zwei effektive Analgetika im Wirkungsvergleich. *Fortschr Med* 1989; **107**: 385–389.

23 Bernatzky G, Jurna I. Intrathecal injection of codeine, buprenorphine, tilidine, tramadol and nefopam depresses the tail-flick response in rats. *Eur J Pharmac* 1986; **120**: 75–80.

24 Hennies H-H, Friderichs E, Schneider J. Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. *Drug Res* 1988; **38**: 877–880.

25 Rohdewald P, Granitzki HW, Neddermann E. Comparison of the analgesic efficacy of metamizole and tramadol in experimental pain. *Pharmacology* 1988; **37**: 209–217.

26 Vogel W, Burchardi H, Sihler K, Valic L. Über die Wirkung von Tramadol auf Atmung und Kreislauf. *Drug Res* 1978; **28**: 183–186.

27 Flohe L, Arend I, Cogal A, Richter W, Simon W. Klinische Prüfung der Abhängigkeitsentwicklung nach Langzeitapplikation von Tramadol. *Drug Res* 1978; **28**: 213–217.

28 Richter W, Barth H, Flohe L, Giertz H. Klinische Untersuchung zur Abhängigkeitsentwicklung bei oraler Therapie mit Tramadol. *Drug Res* 1985; **35**: 1742–1744.

29 Magni G. The use of antidepressants in the treatment of chronic pain. *Drugs* 1991; **42**: 730–748.

30 France RD, Houpt JL, Ellinwood EH. Therapeutic effects of antidepressants in chronic pain. *Gen Hosp Psychiatry* 1984; **6**: 55–63.

31 Walsh TD. Antidepressants in chronic pain. *Clin Neuropharmac* 1983; **6**: 271–295.

32 Bromm B, Meier W, Scharein E. Imipramine reduces experimental pain. *Pain* 1986; **25**: 245–257.

33 Ardid D, Eschalier A, Lavarenne J. Evidence for a central but not a peripheral analgesic effect of clomipramine in rats. *Pain* 1991; **45**: 95–100.

34 Eide K, Hole K. Acute and chronic treatment with selective serotonin uptake inhibitors in mice: effects on nociceptive sensitivity and response to 5-methoxy-N,N-dimethyltryptamine. *Pain* 1988; **32**: 333–340.

35 Fialip RG, Makambila MC, Rigal F, Devoize JL, Varoquax O, Eschalier A. Chronic administration of clomipramine inhibits morphine hot-plate analgesia. *Life Sci* 1986; **38**: 1097–1103.

36 Sacerdote P, Brini A. Mantegazza P, Panerai AE. A role for serotonin and beta-endorphin in the analgesia induced by some tricyclic antidepressant drugs. *Pharmac Biochem Behav* 1987; **26**: 153–158.

37 Lintz W, Barth H, Osterloh G, Schmidt-Bothelt E. Bioavailability of enteral tramadol formulations. 1st communication: capsules. *Arzneimittelforschung* 1986; **36**: 1278–1283.

38 ASTA-Pharma AG, Frankfurt, FRG. *Investigational drug brochure, D16949 Anpirtoline*, 1989.

39 Suttfin TA, De Vance CL, Jusko WJ. The analysis and disposition of imipramine and its active metabolites in man. *Psychopharmacologia* (Berlin) 1984; **82**: 310–317.

40 Becker DE, Yingling CD, Fein G. Identification of pain, intensity and P300 components in the pain evoked

potential. *Electroenceph clin Neurophysiol* 1993; **88**: 290–301.
41 Reading EA. Testing pain mechanisms in persons in pain. In *Textbook of pain*, eds Wall PD, Melzack R, Edinburgh: Churchill Livingstone, 1989; 269–280.
42 Bundesgesundheitsamt. *Katalog unerwünschter Arzneimittelwirkungen (UAW) einschließlich der deutschen Übersetzung der WHO-Adverse Reaction Terminology*, Version 1.0. Bundesgesundheitsamt, 14171 Berlin, 1988.
43 Klose R, Erhart A, Jung R. Der Einfluß von Buprenorphin und Tramadol auf die CO_2-Antwort in der postoperativen Phase nach Allgemeinanästhesie. *Anästh Intensivther Notfallmed* 1982; **17**: 29–34.
44 Lehmann KA, Jung C, Ribbert N, van Heis R, Daub D. Postoperative "On-Demand"-Analgesie: eine vergleichende Untersuchung mit 5 Schmerzmitteln. *Anaesthetist* 1983; **32**: 162–163.
45 Friedel B. Die Wirkung von Tramadol auf das Elektroenzephalogramm und Elektronystagmogramm. *Drug Res* 1978; **28**: 187–189.
46 Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In *The pharmacological basis of therapeutics*, eds Gilman AG, Goodman LS, Rall TW, Murad F, New York: Macmillan, 1985; 387–445.
47 Weisenberg M. Cognitive aspects of pain. In *Textbook of pain*, eds Wall PD, Melzack R, Edinburgh: Churchill Livingstone, 1989; 231–241.
48 Craig KD. Emotional aspects of pain. In *Textbook of pain*, eds Wall PD, Melzack R, Edinburgh: Churchill Livingstone, 1989; 220–230.
49 Kobal G, Hummel T. Effects of flupirtine on the pain-related evoked potential and the spontaneous EEG. *Agents Actions* 1988; **23**: 117–119.
50 Hoesl M. *Beeinflußung schmerzkorrelierter evozierter Potentiale durch Analgetika und Benzodiazepine*. Medical Thesis University of Erlangen-Nürnberg, Germany, 1989.
51 Bromm B, Meier W. The intracutaneous stimulus: A new pain model for algesimetric studies. *Meth find exp clin Pharmac* 1984; **6**: 405–410.
52 Gracely RH. Methods of testing pain mechanisms in normal man. In *Textbook of pain*, eds Wall PD, Melzack R, Edinburgh: Churchill Livingstone, 1989; 257–268.
53 Dong WK, Chudler EH, Martin RH. Physiological properties of intradental mechanoreceptors. *Brain Res* 1985; **334**: 389–395.
54 Sessle BJ. Is the tooth pulp a 'pure' source of noxious input? In *Advances in pain research and therapy*, Vol. 3, eds Bonica JJ, Liebeskind JC, Albe-Fessard DG, New York: Raven Press. 1979; 245–260.

(Received 14 April 1993, accepted 22 November 1993)