Effects of flurbiprofen enantiomers on pain-related chemo-somatosensory evoked potentials in human subjects

JÖRN LÖTSCH, GERD GEISSLINGER, PARVANEH MOHAMMADIAN, KAY BRUNE & GERD KOBAL
Department of Experimental and Clinical Pharmacology and Toxicology, University of Erlangen-Nürnberg,
Universitätsstrasse 22, D-91054 Erlangen, Germany

- 1 The aim of the study was to investigate the analgesic effects of flurbiprofen enantiomers using an experimental pain model based on both chemo-somatosensory event-related potentials (CSSERP) and subjective pain ratings.
- 2 Healthy female volunteers ($n = 16$, age 23–36 years) participated in a placebo-controlled, randomised, double-blind, four-way crossover study. Single doses of (S)-flurbiprofen (50 mg), (R)-flurbiprofen (50 and 100 mg) and placebo were administered orally. Measurements were taken before and 2 h after administration of the medications. During each measurement, 32 painful stimuli of gaseous carbon dioxide (200 ms duration, interval approximately 30 s) of two concentrations (60 and 65% CO₂ v/v) were applied to the right nostril. EEG was recorded from five positions and CSSERP were obtained in response to the painful CO₂-stimuli. Additionally, subjects rated the perceived intensity of the painful stimuli by means of a visual analogue scale (VAS).
- 3 The CSSERP-amplitude P2, a measure of analgesic effect, decreased after administration of both (R)- and (S)-flurbiprofen, while it increased after placebo. This was statistically significant at recording positions C4 ($P < 0.01$) and Fz ($P < 0.05$). The analgesia-related decreases in evoked potential produced by (R)-flurbiprofen were dose-dependent. Comparing similar doses of (R)- and (S)-flurbiprofen, the decrease in CSSERP-amplitudes produced by the (S)-enantiomer was somewhat more pronounced, indicating a higher analgesic potency.
- 4 The present data indicate that both enantiomers of flurbiprofen produce analgesic effects. Since (R)-flurbiprofen caused only little toxicity in rats as compared with the (S)-enantiomer or the racemic compound, a reduction of the quantitatively most important side effects in the gastrointestinal tract might be achieved by employing (R)-flurbiprofen in pain therapy.

Keywords chemo-somatosensory event-related potentials analgesics flurbiprofen enantiomers

Introduction

Flurbiprofen [(±)-2-fluoro- α -methyl-4-biphenylacetic acid], a chiral 2-arylpropionic acid derivative, is an anti-inflammatory and analgesic drug. The anti-inflammatory activity is mediated by inhibition of prostaglandin synthesis, which is exerted mainly by the (S)-enantiomer, whereas antinociceptive effects are exerted by both flurbiprofen enantiomers [1–3]. So far, in humans only the racemate and the (S)-enantiomer have been investigated. (S)-flurbiprofen

appeared to be significantly more effective than the racemic compound in patients with postepisiotomy pain [4]. Data demonstrating an analgesic effect of (R)-flurbiprofen in man are lacking. A possible analgesic effect of (R)-flurbiprofen would be of clinical relevance, as (R)-flurbiprofen does not cause gastrointestinal lesions in rats [1].

Flurbiprofen enantiomers undergo chiral inversion in dogs and guinea pigs, but not in man [5, 6]. Thus,

Correspondence: Dr med. Jörn Lötsch, Department of Experimental and Clinical Pharmacology and Toxicology, University of Erlangen-Nürnberg, Universitätsstrasse 22, D-91054 Erlangen, Germany

pharmacodynamic effects of flurbiprofen enantiomers in man are not confounded by chiral inversion. The aim of the present exploratory study was to assess the analgesic effects of single doses of 50 mg and 100 mg (R)-flurbiprofen in human volunteers. A placebo controlled double-blind four-way crossover study design was chosen. (S)-flurbiprofen (50 mg) served as reference medication. An experimental pain model based on both chemo-somatosensory event-related potentials (CSSERP) and subjective pain ratings was used. To control for possible non-specific effects of flurbiprofen, a number of other parameters were assessed (i.e. acoustic event-related potentials (AERP), vigilance, frequency bands of the spontaneous EEG, ratings for sedation-related symptoms).

Over the last several years, event-related potentials (ERPs) have become a standard tool for the assessment of nociception. Using a variety of stimulation techniques, ERPs have been shown to correlate well with the ratings of pain intensity [7–20]. Furthermore, event-related potentials have been used to assess the analgesic effects of numerous drugs [15, 21–26]. For example, Kobal and co-workers established an experimental pain model based on chemo-somatosensory event-related potentials (CSSERP) in response to painful stimulation of the nasal mucosa with carbon dioxide [12, 27–30]. These CO₂-stimuli have been demonstrated specifically to excite trigeminal nociceptors [28, 31]. The cerebral sources of these responses have been localised in the somatosensory area SII [32], which is assumed to be a primary projection area for nociceptive afferents [33]. One of the advantages of this technique is that the method is non-invasive and the results seem negligibly influenced by non-analgesic drug effects [24, 30]. So far, this model has been applied in quantifying the analgesic activity of both opioid and non-opioid analgesics [22–25, 34].

Methods

Subjects

Sixteen healthy female volunteers (on oral contraceptives) between 23 and 36 years of age participated in the study. All subjects were within 20% of their ideal body weight which was 58.9 ± 3.5 kg. At the beginning and at the end of the study the subjects' health was ascertained by general clinical examination and routine laboratory tests. Subjects took part in the experiments after having given written informed consent. The study was conducted according to the Declaration of Helsinki on biomedical research involving human subjects. The protocol was approved by the University of Erlangen-Nürnberg Medical Ethics Review Committee.

Study medication

(R)- and (S)-flurbiprofen were kindly supplied by PAZ Arzneimittelentwicklungsgesellschaft mbH

(Frankfurt/Main, Germany) with chemical and optical purities of > 98.5%. (R)-flurbiprofen (lot 1151-A-5-R) and (S)-flurbiprofen (lot 1151-A-5-S) were administered in gelatine capsules of the same size containing either 50 mg (S)-flurbiprofen, or 50 mg or 100 mg (R)-flurbiprofen. Lactose capsules of the same size were used as placebo.

Study design

The study was designed to be exploratory. It followed a randomised, double-blind, four-way crossover design. The subjects participated in four experiments. An interval of at least 5 days served as washout period between the experiments. Following an overnight fast, in each experiment the subjects took single doses of either 50 mg (S)-flurbiprofen, 50 mg (R)-flurbiprofen, 100 mg (R)-flurbiprofen or placebo with 200 ml water. Subjects abstained from caffeine and alcohol for at least 8 h before the experiments started. Each experiment consisted of two testing sessions lasting for approximately 20 min. The sessions took place before and 2 h after administration of the medication. During the experiments, subjects were comfortably seated. To mask switching clicks of the chemical stimulator, white noise of approximately 50 dB SPL was used. In an additional training session which was performed before the actual experiments started, subjects were familiarised with the experimental conditions and procedures. In this session the subjects learned a specific breathing technique (velopharyngeal closure [12]) which avoids air-flow inside the nasal cavity during stimulation.

Painful stimulation of the nasal mucosa

Carbon dioxide was used to elicit painful sensations (stimulus duration 200 ms, interstimulus interval approximately 30 s). To achieve a pure painful stimulation, thus avoiding alternations of mechanical and thermal conditions at the nasal mucosa, pulses of gaseous CO₂ were mixed in a constantly flowing air stream of controlled temperature and humidity (36.5° C, 80% relative humidity). The rise time of the stimulus' concentration pulses was below 20 ms, i.e. it was sufficiently steep to elicit late nearfield event-related potentials. The method is described in detail elsewhere [12]. During each session, 32 stimuli of two concentrations of CO₂, both well above pain-threshold (60 and 65% v/v), were applied in a pseudo-randomised sequence.

Chemo-somatosensory event-related potentials (CSSERP)

The EEG was recorded from five positions of the international 10/20 system (Cz, C3, C4, Fz and Pz) referenced to linked earlobes (A1+A2). Possible blink artefacts were monitored from an additional site (Fp2/A1+A2). Stimulus linked EEG-segments of 2048 ms duration were sampled with a frequency of 250 Hz (band pass 0.2–30 Hz, prestimulus period 540 ms). After analogue-to-digital conversion, the EEG

segments were stored on an IBM compatible computer. Pain-related CSSERPs were obtained by averaging the EEG records linked to the painful CO₂ stimuli separately for each CO₂ concentration and recording position, discarding all eye-blink contaminated records. Amplitudes N1 and P2 of the CSSERPs and their latencies were analysed.

Intensity estimates of painful stimuli

Within 3–4 s after presentation of each CO₂ stimulus, subjects estimated the perceived intensity relative to a standard stimulus (60% CO₂ v/v) which was presented at the beginning of the first session of each experiment. The subjects rated the intensity of the pain by means of a visual-analogue scale displayed on a computer monitor [22]. The intensity of the standard was defined as 100 Estimation Units (EU). For further statistical evaluation, the estimates of individual subjects were averaged separately for each CO₂ concentration and session.

Acoustic event-related potentials

During each session, 20 acoustic stimuli (1 kHz bursts, 50 dB SPL, duration 100 ms, 10 ms rise time) were randomly applied to the left ear via headphones during the intervals between painful stimulations. The analysis of acoustic event-related EEG segments was performed as described for the CSSERPs.

Frequency analyses of the spontaneous EEG

At the beginning of each session spontaneous EEG was recorded over a period of 3 min (30 EEG records of 4096 ms; sampling frequency 125 Hz). These records were submitted to frequency analysis (Fast Fourier Transformation, FFT), discarding all eye-blink contaminated records. The resulting power spectra were averaged and subsequently divided into six frequency bands (delta: 1–3.5 Hz, theta: 3.5–7 Hz, alpha₁: 7–10 Hz, alpha₂: 10–13 Hz, beta₁: 13–18 Hz, beta₂: 18–21 Hz). The integrated power of these bands was used for further statistical evaluation.

Tracking performance

Subjects were required to perform a simple task on a video screen during the intervals between phasic stimuli [22]. Using a joystick, they had to keep a small square inside a larger one, which randomly moved around. By determining how long the subjects lost contact with the independently moving square, it was possible to detect changes in vigilance and/or motor co-ordination (range between 0 and 100% successful performance in tracking). The data were averaged separately for each session.

Plasma concentrations of flurbiprofen

To determine the pharmacokinetic parameters including the rate of absorption of flurbiprofen, venous blood samples were collected before and at 0.25, 0.5,

0.75, 1.25, 1.5, 1.75, 2.25, 4.0, 6.0, 8.0, 10.0 and 24.0 h after administration of the medication. Plasma samples were immediately frozen at –25° C. Concentrations of (R)- and (S)-flurbiprofen were measured by stereoselective high-performance liquid chromatography (h.p.l.c.) as described previously [35]. A plasma concentration of < 2 µg ml⁻¹ at time point 2.25 h was a predefined exclusion criterion for statistical analysis.

Adverse events

Subjects reported all possible physical or psychological effects they could relate to the medication. Additionally, they were required specifically to rate the intensity of 'tiredness', 'sickness', 'vertigo' and 'drowsiness'. Estimates were performed by means of visual-analogue scales (length 100 mm). The end score to the left (0) was defined as 'no such symptom' and the end score to the right (100) as 'symptom experienced at maximum'. These estimates were given by the subjects after each session.

Statistical analysis

SPSS programs were employed for statistical evaluation. To control for interindividual and intertreatment baseline variability, differences between data recorded after and before administration of the drugs were computed. These data were submitted to univariate analyses of variance for repeated measures (MANOVA, within subject factor 'drug'). Greenhouse-Geisser correction for degrees of freedom was employed where appropriate. To determine differences between the drugs, paired *t*-tests were employed only when the MANOVA yielded significant effects of the factor 'drug'. A *P* value below 0.05 was defined as statistically significant. In addition, 95% confidence intervals for differences were calculated.

Results

Sixteen subjects completed the study. One subject was excluded from statistical evaluation due to an insufficient rate of absorption of flurbiprofen (1.72 µg ml⁻¹ at 2.25 h after administration of 100 mg (R)-flurbiprofen). For technical reasons, the data of two subjects were incomplete and subsequently rejected by the MANOVA.

Chemo-somatosensory event-related potentials (CSSERP)

In general, responses to the stronger CO₂-stimuli (65% v/v) were greater than those to the weaker stimuli (60% v/v). Figure 1 shows the effects of the study medication on CSSERPs in a representative subject. MANOVA revealed significant effects of the factor 'drug' for the amplitude P2 at central and frontal recording positions in response to the stronger CO₂

Figure 1 Chemo-somatosensory event-related potentials (CSSERP) at recording position C4 (referenced against A1+A2) in a representative subject before (thin lines) and 2 h after administration of the study medication (bold lines). A schematic drawing of CSSERP peaks N1 and P2 and of the recording positions is shown in the inset.

stimuli (C4: $F = 4.55$, $df = 33/3$, $P = 0.009$, observed power at 5% level: 0.84; Fz: $F = 2.95$, $df = 33/3$, $P = 0.047$, observed power at 5% level: 0.64; Figure 2). This amplitude decreased most after administration of 100 mg (R)-flurbiprofen followed by 50 mg (S)-flurbiprofen. The effects were smaller with 50 mg (R)-flurbiprofen. In contrast, after placebo the amplitude P2 increased. When computing relative changes, amplitude P2 decreased after administration of 100 mg (R)-flurbiprofen by 36%, after 50 mg (S)-flurbiprofen by 22%, after 50 mg (R)-flurbiprofen by 8%, whereas this amplitude increased after placebo by 14%.

Comparing the study medications with each other (Table 1), t -tests revealed that, firstly, all flurbiprofen doses produced a significant decrease of P2 relative to placebo, and secondly, the decrease of P2 was more pronounced after administration of 100 mg (R)-flurbiprofen than after administration of 50 mg (R)-flurbiprofen. However, the differences between 50 mg (S)- and (R)-flurbiprofen did not reach statistical significance. Confidence intervals for differences are given in Table 1.

No systematic changes were observed in the latencies of N1 and P2. Latencies increased after 50 mg (R)-flurbiprofen, 50 mg (S)-flurbiprofen and placebo. In contrast, they decreased after 100 mg (R)-flurbiprofen. Significant effects of the MANOVA-factor

'drug' were observed for the latency of N1 at recording position Cz ($P = 3.21$, $df = 33/3$, $P = 0.036$, observed power at 5% level: 0.69) in response to the stronger CO₂ stimuli, and for P2 at recording positions Cz ($F = 4.26$, $df = 33/3$, $P = 0.012$, observed power at 5% level: 0.82) and C4 ($F = 3.77$, $df = 33/3$, $P = 0.02$, observed power at 5% level: 0.76) in response to the weaker CO₂ stimuli.

Intensity estimates of painful stimuli

The estimated intensity of the painful stimuli depended on the concentration of CO₂: the stronger CO₂ stimuli (65% v/v) were rated higher than the weaker stimuli (60% v/v; [29]). Thus, subjects were able to discriminate the CO₂ concentrations. The changes produced by the study medications were generally small and showed a large variance which was approximately four-fold larger than the corresponding differences of mean values. The statistics revealed no significant effect of the study medication.

Acoustic event-related potentials

In contrast to the pain-related responses, acoustic event-related potentials did not change in relation to the study medication.

Figure 2 Mean and s.e. mean of the amplitude P2 of chemo-somatosensory event-related potentials (CSSERP), in relation to baseline measures (differences between measures obtained 2 h after drug administration and baseline). All flurbiprofen treatments were significantly different from placebo. □ placebo, ▨ 50 mg (R)-flurbiprofen, ▩ 50 mg (S)-flurbiprofen, ■ 100 mg (R)-flurbiprofen.

Table 1 Differences of CSSERP amplitude P2 (means [µV]) in response to the stronger CO₂ stimuli (65% v/v) at recording position C4 following oral administration of 50 mg (R)-flurbiprofen, 50 mg (S)-flurbiprofen, 100 mg (R)-flurbiprofen or placebo to 16 healthy human subjects. Statistical comparison of differences between treatments using paired *t*-tests. The mean differences [µV] and their statistical significance are presented (NS = not significant). 95% confidence intervals for differences are given in square brackets

	Placebo	50 mg (R)-flurbiprofen	50 mg (S)-flurbiprofen
Placebo	—	—	—
50 mg (R)-flurbiprofen	5.5 µV, <i>P</i> < 0.05 [0.3 to 10.6 µV]	—	—
50 mg (S)-flurbiprofen	6.0 µV, <i>P</i> < 0.05 [0.6 to 11.5 µV]	0.8 µV, NS [−3.2 to 4.7 µV]	—
100 mg (R)-flurbiprofen	10.1 µV, <i>P</i> < 0.01 [3.0 to 17.1 µV]	5.2 µV, <i>P</i> < 0.05 [0.4 to 10.0 µV]	3.9 µV, NS [−2.0 to 9.8 µV]

Figure 3 Mean and s.e. mean of the amplitude N1 of chemo-somatosensory event-related potentials (CSSERP), in relation to baseline measures (differences between measures obtained 2 h after drug administration and baseline). No significant differences between the study medications were observed. □ placebo, ▨ 50 mg (R)-flurbiprofen, ▩ 50 mg (S)-flurbiprofen, ■ 100 mg (R)-flurbiprofen.

Frequency analyses of the spontaneous EEG

No effects of the study medications on spontaneous EEG were observed.

Tracking performance

The tracking performance generally increased during the experiments. No differences between the study medications were observed.

Plasma concentrations of flurbiprofen

The pharmacokinetic parameters of the flurbiprofen-enantiomers are published elsewhere [5]. Neither (R)-nor (S)-flurbiprofen was inverted to its optical antipode to a measurable extent. At 2.25 h, mean plasma concentrations ($\pm$ s.d.) were $6.39 \pm 2.20 \mu\text{g ml}^{-1}$ (S)-flurbiprofen, $6.91 \pm 1.02 \mu\text{g ml}^{-1}$ (R)-flurbiprofen and $11.52 \pm 2.84 \mu\text{g ml}^{-1}$ (R)-flurbiprofen after administration of 50 mg (S)-flurbiprofen and 50 mg and 100 mg (R)-flurbiprofen, respectively.

Adverse events

No effects of the MANOVA-factor 'drug' on the ratings for 'tiredness', 'drowsiness', 'sickness' and 'vertigo' could be observed.

Discussion

The present results demonstrate that both enantiomers of flurbiprofen established analgesic effects according to the experimental human pain model. This was indicated by the decrease of CSSERP amplitude P2 [16, 27, 36]. It has previously been demonstrated that event-related potentials represent an objective tool for assessment of pain and analgesic effects [7–26]. Thus, our data indicate the presence of analgesic effects of both flurbiprofen enantiomers. The specificity of these effects is additionally sustained by the lack of drug effects on acoustic ERPs, spontaneous EEG, the subjects' tracking performance and the ratings for 'tiredness', 'drowsiness', 'sickness' and 'vertigo'. Changes in CSSERP amplitudes were found largest with 100 mg (R)-flurbiprofen, which reduced amplitude P2 by 36%. Compared with other analgesics investigated with the same model, the magnitude of this effect was superior to the effects produced by 800 mg ibuprofen [25] and 1000 mg acetylsalicylic acid [22] and was comparable with the effects observed after injection of 30 mg pentazocine [22] or 0.2 mg fentanyl [37] or after oral administration of 200 mg flupirtine [23]. However, there is a need to compare (R)-flurbiprofen directly with other non-opioid analgesics like paracetamol or with opioids. Chiral inversion of either (R)- or (S)-flurbiprofen to its optical antipode did not occur to a measurable extent [5]. Thus, the analgesic effects observed after administration of (R)-flurbiprofen have to be attributed to this enantiomer. However, the mechanism of the analgesic effects of (R)-flurbiprofen still remains unclear. Possibly, the inhibition of brain cyclooxygenase by (R)-flurbiprofen as shown in rat experiments takes part in this effect [38, 39].

The analgesic activity of (R)-flurbiprofen as indicated by the reduction of CSSERP amplitudes appeared to be dose-dependent. However, since there are only two dosages, the type of dose-dependency cannot be specified. Comparing similar doses of (R)- and (S)-flurbiprofen, the analgesia related changes in evoked potentials produced by the (S)-enantiomer seem to be more pronounced. Although in the present study these differences did not reach statistical significance, they are sustained by other reports of a smaller analgesic efficacy of the (R)-enantiomer [2, 3]. As indicated by our data, the analgesic efficacy of 50 mg (S)-flurbiprofen might be located between that of 50 mg and 100 mg (R)-flurbiprofen. The probably higher analgesic activity of the (S)-enantiomer relative to the (R)-enantiomer might be attributed to the additional cyclooxygenase inhibitory action of the (S)-enantiomer [38, 39].

With respect to the topographical pattern of changes in CSSERP amplitudes, most pronounced

decreases were observed at recording position C4 and, to a smaller degree, at Fz. A similar pattern showing effects predominantly at central and frontal recording positions was observed with other non-opioid analgesics [22, 25] and seems to be typical for analgesics of this class. This suggests a specific modulation of the CSSERPs' cortical generator by non-opioid analgesics [32]. In contrast, when investigating opioids, especially with agonist action at μ -opioid receptors (pentazocine [22], fentanyl [37]), a decrease in CSSERP amplitudes was observed at all recording positions including parietal sites. Further studies, possibly with magnetic source-imaging, should clarify the meaning of these topographical patterns and the underlying changes in the cortical generator populations.

The effects of both flurbiprofen enantiomers observed in the CSSERP amplitudes were not reflected by the subjective pain ratings. Although the subjects were able to differentiate among CO₂ concentrations, the ratings did not indicate a drug effect. Previous reports demonstrate the large variance in pain ratings during the measurement of the effects of NSAIDs in experimental pain models. For example, after administration of acetylsalicylic acid [22] or ibuprofen [25] CSSERP amplitudes decreased, whereas the decrease in intensity estimates was not statistically significant. In another study, the effects of acetylsalicylic acid and paracetamol only became statistically significant after the subjects were separated into 'responders' and 'non-responders' [40], which was not possible in the present study due to the small number of subjects. In another study, where non-opioid and opioid analgesics were compared in the same experiments, intensity estimates were decreased by pentazocine, whereas the evaluation of estimates after administration of acetylsalicylic acid revealed only a trend, but no statistically significant changes, towards lower pain ratings [22]. To confirm the analgesic effects of NSAIDs using pain ratings, the number of subjects should be increased approximately four-fold. Thus, for relative low analgesic effects compared with the action of opioids, CSSERP amplitudes seem to be a more sensitive indicator than subjective data. One of the reasons for the higher variance of subjects' estimates is their vulnerability by non-specific effects. It has been demonstrated previously that CSSERPs were not reduced by benzodiazepines such as diazepam [30] or tricyclic antidepressants such as imipramine [24]. In contrast, the pain ratings were decreased after administration of imipramine by the sedative effects of this drug which produced also an increase in 'tiredness', a decrease of the tracking performance, and an increase in the power density of the theta- and alpha-band of the spontaneous EEG [24].

In conclusion, the present data indicate that both enantiomers of flurbiprofen produce analgesic effects as defined in an experimental human pain model. This confirms suggestions of a dissociation between anti-inflammatory and analgesic effect of NSAIDs [41]. The data also suggest that (S)-flurbiprofen could be used to inhibit inflammation and pain in intensive inflammation, while the (R)-enantiomer could be used

for the treatment of pain only. Since (R)-flurbiprofen caused less toxicity in rats than the (S)-enantiomer or the racemic compound [1, 42], a reduction of gastrointestinal tract side effects might be achieved by

employing (R)-flurbiprofen in pain therapy. There is, however, a need to compare the effectiveness and side effects of flurbiprofen enantiomers in patients suffering from different types of painful diseases.

References

- 1 Brune K, Beck WS, Geisslinger G, Menzel-Soglowek S, Peskar BM, Peskar BA. Aspirin-like drugs may block pain independently of prostaglandin synthesis inhibition. *Experientia* 1991; **47**: 257–261.
- 2 Geisslinger G, Ferreira SH, Menzel S, Schlott D, Brune K. Antinociceptive actions of R(-) flurbiprofen—a non-cyclooxygenase inhibiting 2-arylpropionic acid—in rats. *Life Sci* 1994; **54**: PL173–PL177.
- 3 Malmberg AB, Yaksch TL. Antinociception produced by spinal delivery of the S and R enantiomer of flurbiprofen in the formalin test. *Eur J Pharmacol* 1994; **256**: 205–209.
- 4 Sunshine A, Zighelboim J, Olson N, Laska E. Flurbiprofen, flurbiprofen dextrorotatory component (BTS 24332), and placebo in post episiotomy pain. *Clin Pharmacol Ther* 1987; **42**: 162.
- 5 Geisslinger G, Lötsch J, Menzel S, Kobal G, Brune K. Stereoselective disposition of flurbiprofen in healthy subjects following administration of the pure enantiomers. *Br J Clin Pharmacol* 1994; **37**: 392–394.
- 6 Menzel-Soglowek S, Geisslinger G, Beck WS, Brune K. Variability of inversion of (R)-flurbiprofen in different species. *J Pharm Sci* 1992; **81**: 888–891.
- 7 Chapman CR. Evoked potentials as correlates of pain and pain relief in man. *Agents Actions Suppl* 1986; **19**: 51–73.
- 8 Carmon A, Dotan Y, Sarne Y. Correlation of subjective pain experience with cerebral evoked responses to noxious thermal stimulations. *Exp Brain Res* 1978; **33**: 445–453.
- 9 Kakigi R, Shibasaki H, Ikeda A. Pain-related somatosensory evoked potentials following CO₂ laser stimulation in man. *Electroencephalogr Clin Neurophysiol* 1989; **74**: 139–146.
- 10 Wright A, Davies II. The recording of brain evoked potentials resulting from intra-articular focused ultrasonic stimulation: a new experimental model for investigating joint pain in humans. *Neurosci Lett* 1989; **97**: 145–150.
- 11 Chatrian GE, Canfield RC, Knauss TA, Eegt EL. Cerebral responses to electrical tooth pulp stimulation in man. An objective correlate of acute experimental pain. *Neurology* 1975; **25**: 745–757.
- 12 Kobal G. Pain-related electrical potentials of the human nasal mucosa elicited by chemical stimulation. *Pain* 1985; **22**: 151–163.
- 13 Kobal G, Hummel C. Cerebral chemosensory evoked potentials elicited by chemical stimulation of the human olfactory and respiratory nasal mucosa. *Electroencephalogr Clin Neurophysiol* 1988; **71**: 241–250.
- 14 Bromm B, Neitzel H, Tecklenburg A, Treede RD. Evoked cerebral potential correlates of C-fibre activity in man. *Neurosci Lett* 1983; **43**: 109–114.
- 15 Bromm B, Scharein E. A sensitive method to evaluate effects of analgesics in man. *Methods Find Exp Clin Pharmacol* 1983; **5**: 545–551.
- 16 Chen AC, Chapman CR, Harkins WE. Brain evoked potentials are functional correlates of induced pain in man. *Pain* 1979; **6**: 365–374.
- 17 Becker DE, Yingling CD, Fein G. Identification of pain, intensity and P300 components in the pain evoked potential. *Electroencephalogr Clin Neurophysiol* 1993; **88**: 290–301.
- 18 Kunde V, Treede RD. Topography of middle-latency somatosensory evoked potentials following painful laser stimuli and non-painful electrical stimuli. *Electroencephalogr Clin Neurophysiol* 1993; **88**: 280–289.
- 19 Tarkka IM, Treede RD. Equivalent electrical source analysis of pain-related somatosensory evoked potentials elicited by a CO₂ laser. *J Clin Neurophysiol* 1993; **10**: 513–519.
- 20 Chen AC. Human brain measures of clinical pain: a review. I. Topographic mappings. *Pain* 1993; **54**: 115–132.
- 21 Arendt Nielsen L, Oberg B, Bjerring P. Analgesic efficacy of i.m. alfentanil. *Br J Anaesth* 1990; **65**: 164–168.
- 22 Kobal G, Hummel C, Nuernberg 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.
- 23 Hummel T, Friedmann T, Pauli E, Niebch G, Borbe HO, Kobal G. Dose-related analgesic effects of flupirtine. *Br J Clin Pharmacol* 1991; **32**: 69–76.
- 24 Hummel T, Hummel C, Friedel I, Pauli E, Kobal G. A comparison of the antinociceptive effects of imipramine, tramadol and anipriline. *Br J Clin Pharmacol* 1994; **37**: 325–333.
- 25 Kobal G, Hummel C, Gruber M, Geisslinger G, Hummel T. Dose-related effects of ibuprofen on pain-related potentials. *Br J Clin Pharmacol* 1994; **37**: 445–452.
- 26 Bromm B, Ganzel R, Herrmann WM, Meier W, Scharein E. Pentazocine and flupirtine effects on spontaneous and evoked EEG activity. *Neuropsychobiology* 1986; **16**: 152–156.
- 27 Handwerker HO, Kobal G. Psychophysiology of experimentally induced pain. *Physiol Rev* 1993; **73**: 639–671.
- 28 Steen KH, Anton F, Reeh PW, Handwerker HO. Sensitization and selective excitation by protons of nociceptive nerve endings in rat skin, *in vitro*. *Pflügers Arch* 1990; **415**: R106.
- 29 Anton F, Euchner I, Handwerker HO. Psychophysical examination of pain induced by defined CO₂ pulses applied to the nasal mucosa. *Pain* 1992; **49**: 53–60.
- 30 Thürauf N, Ditterich W, Kobal G. Dose-related effects of a benzodiazepine on event-related potentials elicited by painful stimuli in man. *Br J Clin Pharmacol* 1994; **38**: 545–556.
- 31 Thürauf N, Hummel T, Kettenmann B, Kobal G. Nociceptive and reflexive responses recorded from the human nasal mucosa. *Brain Res* 1993; **629**: 293–299.
- 32 Huttunen J, Kobal G, Kaukoranta E, Hari R. Cortical responses to painful CO₂ stimulation of nasal mucosa; a magnetoencephalographic study in man. *Electroencephalogr Clin Neurophysiol* 1986; **64**: 347–349.
- 33 Chudler EH, Dong WK, Kawakami Y. Tooth pulp evoked potentials in the monkey: Cortical surface and intracortical distribution. *Pain* 1985; **22**: 221–223.

- 34 Kobal G, Hummel T. Effects of flupirtine on the pain-related evoked potential and the spontaneous EEG. *Agents Actions* 1988; **23**: 117–119.
- 35 Geisslinger G, Menzel Soglowek S, Schuster O, Brune K. Stereoselective high-performance liquid chromatographic determination of flurbiprofen in human plasma. *J Chromatogr* 1992; **573**: 163–167.
- 36 Chen AC, Chapman CR. Aspirin analgesia evaluated by event-related potentials in man: possible central action in brain. *Exp Brain Res* 1980; **39**: 359–364.
- 37 Kobal G, Hummel T, Hoesl M. Pain-related electrical evoked potentials by chemical stimuli: Effects of fentanyl. In *Advances in pain research and therapy*, eds Lipton S, Tunks Zoppi M. New York: Raven Press, 1989: 95–98.
- 38 Brune K, Geisslinger G, Menzel Soglowek S. Pure enantiomers of 2-arylpropionic acids: tools in pain research and improved drugs in rheumatology. *J Clin Pharmacol* 1992; **32**: 944–952.
- 39 Peskar BM, Kluge S, Peskar BA, Menzel-Soglowek S, Brune K. Effects of pure enantiomers of flurbiprofen in comparison to racemic flurbiprofen on eicosanid release from various rat organs *ex vivo*. *Prostaglandins* 1991; **42**: 515–531.
- 40 Bromm B, Herrmann MW, Scharein E. Zur analgetischen Wirksamkeit von Paracetamol und Acetylsalicylsäure im experimentellen Schmerzmodell. *Schmerz/Pain/Douleur* 1988; **9**: 5–11.
- 41 McCormack K, Brune K. Dissociation between the antinociceptive and anti-inflammatory effects of the nonsteroidal anti-inflammatory drugs. *Drugs* 1991; **41**: 533–547.
- 42 Wechter WJ, Bigornia AE, Murray ED Jr, Levine BH, Young JW. *Rac*-flurbiprofen is more ulcerogenic than its (S)-enantiomer. *Chirality* 1993; **5**: 492–494.

(Received 25 January 1995,
accepted 12 June 1995)