Comparison of Two Different Preparations of Ibuprofen with Regard to the Time Course of Their Analgesic Effect

A randomised, placebo-controlled, double-blind cross-over study using Laser somatosensory evoked potentials obtained from UV-irritated skin in healthy volunteers

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Summary

In the treatment of painful conditions the time to onset of a drug's analgesic effect is of great relevance. Plain ibuprofen acid (Ibu, CAS 15687-27-1) is relatively slowly absorbed after oral administration (t_{max} is about 90-120 min). If, however, ibuprofen is given in form of a lysine salt, absorption is much quicker. It has been shown in pharmacokinetic studies that the maximum plasma concentration after administration of an ibuprofen lysine tablet (IbuLys) is reached at about 35 min after oral administration.

The aim of this study was to evaluate the onset and extent of the analgesic effect of 400 mg ibuprofen administered as marketed ibuprofen lysine tablets (two tablets of Dolormin® as a single dose) in comparison with standard Ibu tablets (two tablets as a single dose) and placebo (Plc) utilising the objective, quantitative (high resolution) method of Laser algesimetry. The N1-P2 peak-to-peak amplitude of the Laser-induced somatosensory evoked potentials (LSEPs) – measured during the first two hours after administration of study drugs – was the main efficacy parameter for the onset of the analgesic effects. The values obtained during 5 h after administration of the study drugs were used to measure the extent of the analgesic effects.

As a main result with respect to the *onset of analgesic action*, the reduction of the N1-P2 peak-to-peak amplitude was significantly and relevantly more pronounced during the first 2 h after administration of IbuLys than after Ibu (IbuLys vs. Plc: $p \leq 0.0020$, IbuLys vs. Ibu: $p \leq 0.0366$). During the same time the amplitudes of the single N1-components of the LSEPs were also significantly smaller after IbuLys than after Plc ($p \leq 0.0031$) whereas the difference between plain Ibu and Plc was not significant ($p \leq 0.1027$).

As a measure of the *extent of analgesic action*, the N1-P2 peak-to-peak amplitudes recorded during 5 h after medication were more effectively reduced by IbuLys than by Ibu (IbuLys vs. Plc: $p \leq 0.0001$, IbuLys vs. Ibu: $p \leq 0.0041$, Ibu vs. Plc: p (0.383). The reduction of the amplitudes of the single N1-components by IbuLys was significant in comparison to Plc ($p \leq 0.0031$), but not in comparison to Ibu. During the time of 5 h after medication the attenuating (analgesic) effect of IbuLys on the amplitude of the P2 component of the LSEPs was stronger than that of Plc ($p \leq 0.0053$) and stronger than that of Ibu ($p \leq 0.0058$).

In summary IbuLys was significantly superior to Ibu with respect to the onset and extent of the analgesic effect.

Key words

- CAS 15687-27-1
- Dolormin®
- Ibuprofen, analgesic effect, lysine salt, plain
- Laser algesimetry
- Non-steroidal anti-inflammatory drugs
- Somatosensory evoked potentials
- UV-induced hyperalgesia

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Zusammenfassung

Vergleich von zwei verschiedenen Ibuprofen-Zubereitungen im Hinblick auf den Zeitverlauf ihrer analgetischen Wirkung / Eine randomisierte, Plazebo-kontrollierte, verblindete Crossover-Studie auf der Grundlage von somatosensorisch evozierten Potentialen von UV-bestrahlter Haut bei gesunden Versuchspersonen

Bei der Behandlung von Schmerzen ist die Geschwindigkeit des Wirkungseintritts eines Analgetikums von großer Bedeutung. Aus der üblichen pharmazeutischen Formulierung, in der Ibuprofen (Ibu, CAS 15687-27-1) als Säure vorliegt, wird die Wirksubstanz relativ langsam resorbiert (t_{max} liegt bei etwa 90–120 min). Wird Ibuprofen jedoch als Ibuprofen-Lysinsalz (IbuLys) verabreicht, beobachtet man das Maximum der Plasmakonzentration des Wirkstoffs bereits nach ca. 35 min.

Das Ziel dieser Studie war es, 400 mg Ibuprofen als Lysinsalz (2 Tabletten Dolormin® als Einzelgabe) gegen 400 mg Standard-Ibuprofen (2 Tabletten als Einzelgabe) und Plazebo (Plc) hinsichtlich der Geschwindigkeit und des Ausmaßes der analgetischen Wirkung mit dem Modell der objektiven und quantitativen (hochauflösenden) Laser-Algesimetrie zu vergleichen. Die Laser-induzierten somatosensorisch evozierten Potentiale (LSEPs), die in den ersten 2 h nach Gabe der Medikation registriert wurden, dienten als Maß für die Geschwindigkeit der analgetischen Wirkung (Hauptzielparameter), die der gesamten 5 h als Parameter für das Ausmaß der analgetischen Wirkung.

***Geschwindigkeit der Wirkung*: Als Hauptergebnis der Studie wurde eine signifikant und relevant stärker mindernde Wirkung von IbuLys auf die Amplituden der LSEPs (N1-P2 peak-to-peak) während der ersten 2 h nach Medikation im Vergleich zu Ibu und Plc gefunden (IbuLys vs. Plc: $p \leq 0.0020$, IbuLys vs. Ibu: $p \leq 0.0366$). Die in dieser Zeitspanne registrierte N1-Komponente der LSEPs wurde durch IbuLys stärker gemindert als durch Plc ($p \leq 0{,}0031$). Die Differenz zwischen Ibu und Plc war nicht signifikant ($p \leq 0.1027$).**

***Ausmaß der Wirkung*: Die Amplituden der LSEPs (N1-P2 peak-to-peak), die über 5 h nach Medikation registriert wurden, zeigten sich durch IbuLys stärker gemindert als durch Ibu (IbuLys vs. Plc: $p \leq 0.0001$, IbuLys vs. Ibu: $p \leq 0.0041$, Ibu vs. Plc: $p \leq 0.383$). Die Minderung der N1-Amplituden der LSEPs durch IbuLys war signifikant deutlicher als durch Plc ($p \leq 0.0031$), aber nicht signifikant stärker als durch Ibu. In der Zeitspanne von 5 h nach Medikation war die Wirkung von IbuLys auf die Amplituden der P2-Komponenten der LSEPs stärker als die von Plc ($p \leq 0.0053$) und stärker als die von Ibu ($p \leq 0.0058$).**

Das Ergebnis dieser Studie zeigt, daß IbuLys der üblichen Formulierung von Ibu hinsichtlich der Geschwindigkeit und des Ausmaßes der analgetischen Wirkung signifikant überlegen ist.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed medications in practice. In the treatment of painful conditions the time to onset of a drug's analgesic effect is of great relevance. Plain ibuprofen acid (Ibu, CAS 15687-27-1) is relatively slowly absorbed after oral administration. The time to maximum plasma concentration of Ibu after oral administration is about 90 to 120 min [1]. This results in a relatively late onset of the analgesic effect of Ibu tablets. If, however, Ibu is given in form of a lysine salt, absorption is much quicker. It has been shown in pharmacokinetic investigations that the maximum plasma concentration after administration of an ibuprofen lysine salt tablet (IbuLys) is reached at about 35 min after oral administration [1]. It is, therefore, expected that the onset of the analgesic effect of Dolormin®[1)] can be observed earlier than that of a standard Ibu preparation.

The aim of this study was to evaluate the onset and extent of the analgesic effect of marketed IbuLys tablets (Dolormin) in comparison with standard Ibu tablets and placebo utilising the objective quantitative (high resolution) method of Laser algesimetry. This method is an alternative to the pure subjective estimations (e.g. with visual analogue scales, VAS) of patients in clinical models of pain management. A CO_2-Laser was used to initiate (Laser) somatosensory evoked potentials (LSEPs), which were recorded from the vertex-EEG. Analgesic properties of drugs can be demonstrated objectively and quantitatively by alterations of the LSEP-parameters – mainly by reductions of their amplitudes. The major advantage of this technique for sensory stimulation with the CO_2-Laser is the fact that heat-sensitive ionic channels of polymodal nociceptors of A-delta (thinly myelinated) and C-fibre (non-myelinated) type are selectively stimulated without any direct skin contact (high receptor specificity). The two main components of the LSEPs, N1 and P2, are evaluated by their peak-to-peak as well as by their single components' amplitudes.

The Laser pain stimulus can be kept constant and is adjusted slightly above the individual pain threshold. Another advantage of using this methodology is that

[1)] Manufacturer: Johnson & Johnson, Woelm Pharma GmbH & Co., Bad Honnef (Germany).

objective recordings of pain by evoked potentials yield smaller variations than subjective ratings. Furthermore, a smaller sample is required to yield sufficient statistical power to the experimental findings.

If pain is elicited by Laser stimuli in normal skin of healthy volunteers this model will mainly reflect acute pain. As acute pain may differ from pain resulting from painful diseases, which mostly involve some degree of hyperalgesia, the skin of the volunteers from which LSEPs were to be derived was pre-treated by UV-irradiation in order to initiate ("full-blown") UV-inflammation connected with (peripheral) hyperalgesia [2].

2. Subjects, materials and methods

2.1. Subjects

Twenty-four healthy (14 male and 10 female) volunteers (age 25–45 years, height 159–192 cm, Body mass index 17–27 kg/m^2) were enrolled after written informed consent. All 24 completed the study and were included in the efficacy analysis. The pre-study medical examination excluded subjects with a history of drug sensitivity or allergy, with a recent history of alcohol or nicotine abuse, who required any regular medication, with an acute dermatitis or other skin lesions, undergoing extreme time shifts (e.g. jet-lag and shift-workers) or who were otherwise unsuitable for participation in the study. The Declaration of Helsinki and the ICH/GCP guidelines were followed in the trial, which was approved by the Ethics Committee of the Bayerische Landesärztekammer, Munich.

2.2. Trial design and treatments

This was a randomised, double-blind, single-dose, placebo-controlled, cross-over single-centre study. Qualified subjects were randomly assigned to receive either 2 tablets containing 200 mg ibuprofen as lysine salt each (IbuLys, Dolormin), 2 tablets containing 200 mg ibuprofen acid each (Ibu, from commercial source) or 2 placebo tablets (Plc) to treat pain induced by Laser on UV-irritated skin.

The treatments were given as a single dose each on three main assessment days which were separated from each other by wash-out periods of one week.

2.3. Pharmacodynamic evaluations

The main assessment days were preceded by pre-study clinical laboratory tests, medical examination, determination of the individual minimal UV-dose producing erythema (minimum erythema dose, MED), application of the 3-fold MED on a small skin area on the back for determination of individual pain thresholds on UV-irritated skin, as well as training on LSEPs. A natural mixture of UVA and UVB radiation was used (six UVA Philips CLEO 40 W and two UVB Philips TL 20 W/12 tubes). 13 to 17 h before start of the measurements of main assessment days a skin area of 5 × 10 cm was UV-irradiated with the 3-fold MED. On assessment days, subjects attended the investigational unit and started their tests always at the same time of the day. The procedures were the same on each assessment day.

Objective and quantitative (high resolution) measurement of pain relief was performed with the Laser-algesimetry. CO_2 Laser stimuli were applied to the skin area which had been UV-irradiated with the 3-fold MED (13 to 17 h before).

The two main evoked potential (EP) components were evaluated with regard to their complex peak-to-peak amplitudes, as well as with regard to the single N1 and P2-components. During stimulation, the subjects were sitting on a chair, with their arms resting on a table in front of them and their head fixed in an ophthalmologic forehead-chin rest for positioning and relaxation of neck muscles, i.e. to avoid myogenic artefacts.

Since alterations in vigilance have an impact on EP amplitudes, there was a need for vigilance control during LSEP assessment. This was done by means of loading the subjects with a pursuit tracking task (PTT) which was performed for the entire period of recording LSEP. For further distraction of the pain measurement procedure and to avoid influences of external disturbing noise, the subjects had to wear earphones which produce 'white noise' (with a sound pressure of 90 dBA).

Due to automatic artefact detection, evaluation of EEG data could be done on-line during registration and SEP-parameters could be derived immediately after completion of data acquisition.

The LSEP N1-P2 peak-to-peak amplitudes were defined as the primary efficacy endpoint for the investigation of analgesic effects. In general analgesic effects of active treatments were expected to result in a reduction of the N1 and P2-amplitudes.

LSEPs from ("full-blown") UV-erythema area were recorded at 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 240 and 300 min after administration of the study drugs. Each of these assessments consisted of several Laser shots to the skin, from which 12 artefact-free vertex-EEG responses were (Gaussian) phase-free filtered and averaged by a computer program.

2.4. Statistical procedures

Efficacy data sets

Efficacy was measured in this trial by Laser-induced somatosensory evoked potentials (LSEPs) from EEG (vertex vs. mastoid = C_z – Cb_1 according to the 10/20 scheme). These are evaluated with respect to the amplitudes of the components N1 and P2.

Primary efficacy variable

N1-P2 peak-to-peak amplitudes (0–2 h) of the LSEPs recorded after administration of IbuLys tablets, plain Ibu tablets and Plc tablets as a parameter of the onset of action. Values recorded after administration of the study medication adjusted for baseline values were used for *confirmatory* analysis.

Secondary efficacy variables

Single N1-amplitudes (0–2 h) and P2-amplitudes (0–2 h) of the LSEPs recorded after administration of IbuLys tablets, plain Ibu tablets and Plc tablets as parameters of the onset of action. Values adjusted for baseline values were used for analyses.

Values (N1-P2 amplitudes and single N1 and P2-amplitudes) of LSEPs recorded 0–5 h after administration of the study medications were used as measures of the overall analgesic efficacy and were evaluated correspondingly. Values adjusted for baseline values were used for analyses.

Analysis of secondary variables

The secondary efficacy variables are analysed as the primary efficacy variables but in an *exploratory* sense.

Calculation of sample size

Minimal detectable differences of mean values	1 µV
Expected standard differences of mean values	1.0657
Number of groups	3
Power	0.8
Alpha	0.05
Minimal no. of subjects	23

For organisation/technical reasons a total of 24 subjects was included.

Statistical model

The parameters of interest (N1-P2 peak-to-peak amplitude, N1-amplitude, P2-amplitude) were described by applying linear mixed regression models. Beside the overall mean (intercept of the regression model) fixed effects were assumed for the classification variables medication, session and for the interaction term medication × session. As variance components the random effects due to subject variability and measurement errors were considered in the model. To adjust for baseline effects the corresponding baseline value was added to the regression model. Period, carry-over as well as sequence effects were not expected, and therefore ignored.

For fixed effects an overall test (F test) for the global hypothesis was applied. After rejection of the global hypothesis a closed testing procedure was used to identify differences between two groups. By this procedure the experiment-wise error rate is controlled in a strong sense. As 3 medication groups were considered, no further adjustment for the p values was necessary.

P values lower than 0.05 were stated as statistically significant. All calculations were performed using the statistical software package SAS® version 8.01 (SAS Institute, Carey, NC, USA).

3. Results

There were no protocol deviations. All 24 subjects included in the study were taken as subject pool. All figures and tables in the following section are based on the complete sample size of 24 subjects.

3.1. Onset of the analgesic effects (0–2 h)

The N1-P2 peak-to-peak amplitudes obtained during the first 2 h after medication was the main target variable – representing the onset of the analgesic effect of the study medications. The reduction of the N1-P2 peak-to-peak amplitudes (Fig. 1 and 2) was significantly and relevantly stronger during the first 2 h after administration of IbuLys than after plain Ibu (IbuLys vs. Plc: $p \leq 0.0020$, IbuLys vs. Ibu: $p \leq 0.0366$).

During the same time the amplitudes of the single N1-components of the LSEPs (Fig. 3) were also significantly smaller after IbuLys than after Plc ($p \leq 0.0031$), whereas the difference between plain Ibu and Plc was not significant ($p \leq 0.1027$).

The P2-components showed no significant differences in all pair-wise comparisons during the first 2 h.

That the drug effects on the N1-component, which reflects more peripheral analgesic effects, were more pronounced than those on the (central) P2-component is in line with the current knowledge that the UV-induced inflammatory hyperalgesia is mainly a peripheral phenomenon with only minor central components.

In addition to these per-protocol analyses the effect on the LSEP amplitudes obtained during the first 30 min after dosing was analysed. IbuLys was more effective during this time than Plc with respect to the N1-P2 peak-to-peak amplitudes of the LSEPs ($p \leq 0.0126$) and with respect to the single N1-amplitudes ($p \leq 0.0036$). IbuLys was also more effective than plain Ibu (N1-P2: $p \leq 0.0249$, single N1: $p \leq 0.0231$).

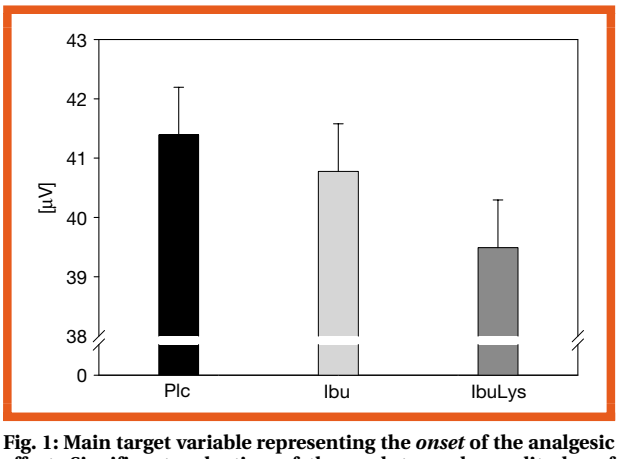

Fig. 1: Main target variable representing the *onset* of the analgesic effect. Significant reduction of the peak-to-peak amplitudes of the Laser-induced somatosensory evoked potentials (LSEPs) obtained from UV-irradiated skin during the first 2 h after medication by IbuLys in comparison to plain Ibu (acid) and Plc. Means and SEM (baseline adjusted values) of measurements taken from 24 subjects at 15, 30, 45, 60, 75, 90, 105 and 120 min after administration of the study drugs.

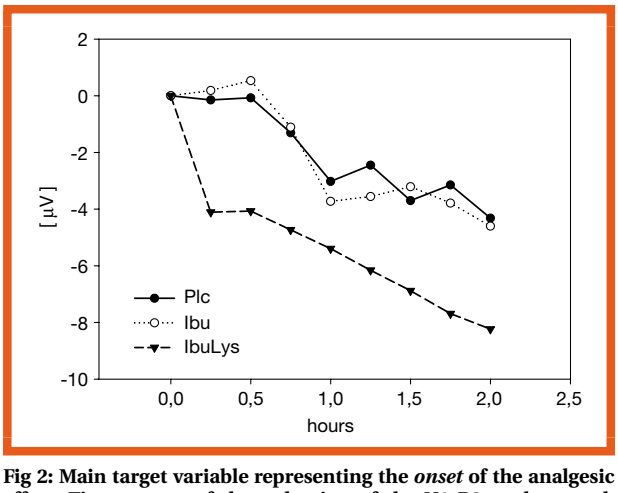

Fig 2: Main target variable representing the *onset* of the analgesic effect. Time course of the reduction of the N1-P2 peak-to-peak amplitudes of the Laser-induced somatosensory evoked potentials (LSEPs) obtained from UV-irradiated skin during the first 2 h after medication by IbuLys in comparison to Ibu and Plc. Means (baseline corrected values) of measurements taken from 24 subjects at 15, 30, 45, 60, 75, 90, 105 and 120 min after administration of the study drugs.

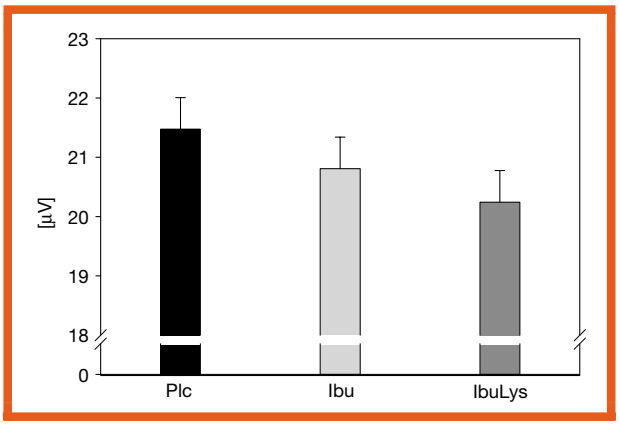

Fig. 3: Secondary efficacy variable representing the *onset* of the analgesic effect. Significant reduction of the amplitudes of the single N1-component of the Laser-induced somatosensory evoked potentials (LSEPs) obtained from UV-irradiated skin during the first 2 h after medication by IbuLys in comparison to Ibu and Plc. Means and SEM (baseline adjusted values) of measurements taken from 24 subjects at 15, 30, 45, 60, 75, 90, 105 and 120 min after administration of the study drugs.

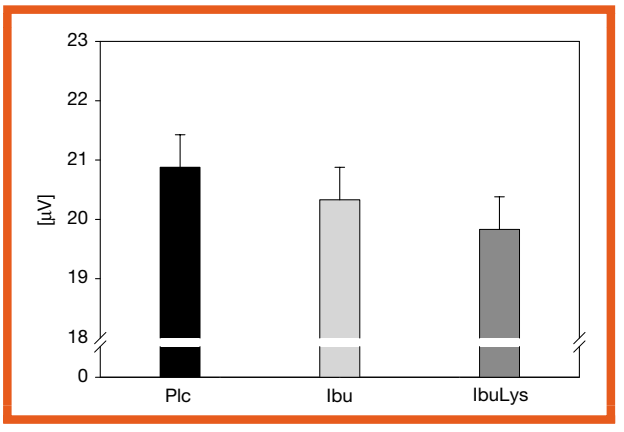

Fig 5: Secondary efficacy variable representing the *extent* of the analgesic effect. Significant reduction of the amplitudes of the single N1-components of the Laser-induced somatosensory evoked potentials (LSEPs) obtained from UV-irradiated skin during five hours after medication by IbuLys in comparison to Ibu and Plc. Means and SEM (baseline adjusted values) of measurements taken from 24 subjects at 15, 30, 45, 60, 75, 90, 105 120, 150, 180, 240 and 300 min after administration of the study drugs.

3.2. Extent of the analgesic effects (0-5 h)

The extent of the analgesic action of the study drugs was measured by means of the reduction of the LSEP amplitudes during the complete 5-h study period after drug intake. The N1-P2 peak-to-peak amplitudes of the LSEPs measured during this time period (Fig. 4) were more effectively reduced by IbuLys than by plain Ibu (IbuLys vs. Plc: $p \leq 0.0001$, IbuLys vs. Ibu: $p \leq 0.0041$, Ibu vs. Plc: $p \leq 0.383$).

The reduction of the amplitudes of the single N1-components of the LSEPs (Fig. 5) by IbuLys was significant in comparison to Plc ($p \leq 0.0031$) but not in comparison to plain Ibu. During the time of 5 h after medication the attenuating effect of IbuLys on the P2-component (Fig. 6) of the LSEPs was stronger than that of Plc ($p \leq 0.0053$) and stronger than that of Ibu ($p \leq 0.0058$). During the 5-h period a greater central contribution to hyperalgesia may have developed due to the repetitive painful Laser shots to the UV-irradiated skin area over this long time period.

It is noteworthy that the significance levels obtained with the 5-h values were generally higher than those resulting from the 2-h values. This holds also for the comparison of IbuLys with plain Ibu. This indicates that the faster onset of the analgesic effect of IbuLys did not result in a shortening of the effect. A survey of all statistical results is given in Tables 1 and 2.

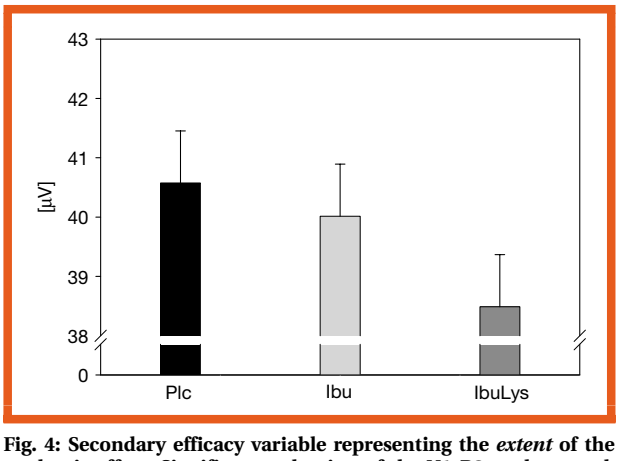

Fig. 4: Secondary efficacy variable representing the *extent* of the analgesic effect. Significant reduction of the N1-P2 peak-to-peak amplitudes of the Laser-induced somatosensory evoked potentials (LSEPs) obtained from UV-irradiated skin during 5 h after medication by IbuLys in comparison to Ibu and Plc. Means and SEM (baseline adjusted values) of measurements taken from 24 subjects at 15, 30, 45, 60, 75, 90, 105 120, 150, 180, 240 and 300 min after administration of the study drugs.

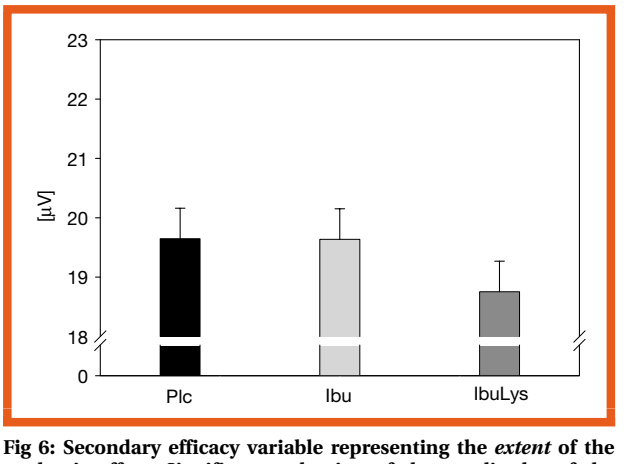

Fig 6: Secondary efficacy variable representing the *extent* of the analgesic effect. Significant reduction of the amplitudes of the single P2-components of the Laser-induced somatosensory evoked potentials (LSEPs) obtained from UV-irradiated skin during 5 h after medication by IbuLys in comparison to Ibu and Plc. Means and SEM (baseline adjusted values) of measurements taken from 24 subjects at 15, 30, 45, 60, 75, 90, 105 120, 150, 180, 240 and 300 min after administration of the study drugs.

Table 1: Statistical values obtained from LSEPs recorded during the first 2 h after medication representing the onset of the analgesic effect.

Parameter (LSEP-amplitudes)	Medication	vs. medication	p value
N1-P2	IbuLys	Plc	*0.0020*
N1-P2	IbuLys	Ibu	*0.0366*
N1-P2	Ibu	Plc	0.3098
N1	IbuLys	Plc	*0.0031*
N1	IbuLys	Ibu	0.1719
N1	Ibu	Plc	0.1027
P2	IbuLys	Plc	0.1415
P2	IbuLys	Ibu	0.1094
P2	Ibu	Plc	0.8937

Table 2: Statistical values obtained from LSEPs recorded during 5 h after medication representing the extent of the analgesic effect.

Parameter (LSEP-amplitudes)	Medication	vs. medication	p value
N1-P2	IbuLys	Plc	*< 0.0001*
N1-P2	IbuLys	Ibu	*0.0041*
N1-P2	Ibu	Plc	0.2830
N1	IbuLys	Plc	*0.0031*
N1	IbuLys	Ibu	0.1566
N1	Ibu	Plc	0.1145
P2	IbuLys	Plc	*0.0053*
P2	IbuLys	Ibu	*0.0058*
P2	Ibu	Plc	0.9774

3.3. Safety

There were no serious or severe adverse events in the study. Four adverse events were reported: one case of stomalgia, one case of heartburn and one case of sore throat under Plc and one case of headache under Ibu (acid).

4. Discussion

The main aim of this study was to investigate whether the observation that the earlier occurrence of the maximum of the ibuprofen plasma concentration after administration of IbuLys tablets in comparison to plain Ibu (acid) [1] causes differences in the onset of action. The method of Laser algesimetry used in this study was able to show such a difference with high statistical significance. This is in part due to the high frequency by which measurements can be taken with this method. As the main variable for the measurement of the onset of the analgesic action of the study drugs, the mean decrease of the N1-P2 amplitudes of the LSEPs recorded during the first 2 h after dosing was chosen. This seemed suitable because some time lag between the rise in the ibuprofen plasma concentration and the analgesic effect was expected (diffusion, time course of decrease of the local prostaglandin levels, reversal of prostaglandin effects) and an observation period of 2 h seemed also to be clinically relevant.

IbuLys reduced the N1-P2 peak-to-peak amplitudes of the LSEPs by 1.90 µV during the first 2 h after dosing and 2.08 µV during the whole 5 h observation period. This means that the analgesic effect of ibuprofen given by this formulation is fully developed during the first 2 h after dosing.

The extent of this effect is considerable. E.g. in preceding studies performed at HPR (data on file) using LSEPs from UV-irritated skin the difference in the N1-P2 peak-to-peak amplitudes was 2.6 µV under a single dose of naproxen sodium (440 mg single dose).

In other preceding studies using LSEPs from capsaicin treated skin the differences in the N1-P2 peak-to-peak amplitudes were: 0.7 µV with a single dose of a new analgesic H1-antagonist and 3.22 µV with long-term administration of the same dose of the same drug [3]. The effect of a long-term administration of a high dose of a specific noradrenaline-reuptake inhibitor on the same parameter was 3.15 µV [4]. A single dose of 25 mg dexketoprofen trometamol reduced the N1-P2 peak-to-peak amplitudes of the LSEPs by 3.0 µV, a single dose of 50 mg of the opioid analgesic tramadol reduced the N1-P2 peak-to-peak amplitudes by 3.5 µV [5].

The pain measurements with the Laser algesimetry were started 13 to 17 h after UV-irradiation. At this time after UV-irradiation the resulting *mechanical* hyperalgesia was found to be fully developed and to remain stable during the following 20 h [2]. The hyperalgesia to Laser stimuli has shown a corresponding time course in our laboratory (72 volunteers, data on file). Thus the measurements presented in this paper have been recorded during a ("full-blown") steady state of the UV-induced hyperalgesia.

As acute pain may differ from pain resulting from painful diseases, which mostly involve some degree of hyperalgesia, the skin of the volunteers from which LSEPs were derived in this study was pre-treated by UV-irradiation in order to initiate hyperalgesia connected with UV-inflammation. The UV-induced inflammation and inflammatory hyperalgesia is known to involve neuropeptides, cytokines, the arachidonic acid cascade [6], bradykinin and other mediators (for review see [7]) – as do other clinical inflammations and states of hyperalgesia.

Neuropeptides play generally an important role in inflammatory processes of the skin (for review see [8]). Neuropeptides released by sensory nerves that innervate the skin and often contact epidermal and dermal cells can directly modulate functions of keratinocytes, Langerhans cells, mast cells, micro-vascular endothelial cells and infiltrating immune cells. UV-irradiation of the rat hind paw induces an increase of spontaneous c-fibre activity and oedema which can be antagonised by a substance P antagonist [9]. A long lasting increase in

skin blood flow initiated by UV-irradiation of rat skin can be reduced by a specific NK1 antagonist, an antagonist of CGRP (calcitonin gene related peptide) and an NO synthase inhibitor [10]. It is in line with these findings that a lowering of skin CGRP, which reaches a minimum 6–12 h after UV-irradiation has been interpreted as a consequence of CGRP-release which starts 2 h after UV-irradiation [11].

Biochemical analysis of suction blister fluids from UV-irritated human skin showed increased levels of prostaglandins, interleukins and histamine (for references see [8]). UV-exposure has been demonstrated to induce production of pro-inflammatory cytokines in vivo as well as in vitro. Keratinocytes release increased amounts of IL1, IL6, IL8, TNFα and granulocyte macrophage colony stimulating factor upon UV-irradiation [12].

UVB which can reach as deep as to reach endothelial cells in vivo, produces in endothelial cells in vitro directly and indirectly (via IL10) an increased release of IL6, IL8 and IL1β with a maximum at 16–24 h after UV-irradiation [13]. The latter is known to be one of the most potent inducers of hyperalgesia, the former to be important for the migration of inflammatory cells. UVB produces in keratinocytes an increase in IL1-expression and IL1-activity [14] and in human skin an increase in IL1 and TNF expression [15] and an increase in the expression of the IL1 receptor in different cultured human cells [16]. IL1, IL6 and TNFα initiate hyperalgesia, which is inhibited by indometacin and is, therefore, probably mediated by prostaglandins [17–19]. IL6, IL1β and TNFα activate a prostaglandin dependent hyperalgesic pathway [19], IL8 seems to activate a sympathetic hyperalgesic pathway [19]. UV-irradiation initiates keratinocytes to produce TNFα and TNFα mRNA [20]. In keratinocytes UVB radiation activates Rel proteins, which are known to play a major role in the transcriptional activation of many genes encoding inflammatory cytokines and adhesion molecules [21].

Involvement of central mechanisms in the UV-induced hyperalgesia has been postulated [22]. Evidence for such an assumption is, however, weak. Moreover, sunburn is not spontaneously painful. Thus a main cause of the induction of central mechanisms of hyperalgesia – i.e. a long lasting nociceptive inflow – which plays an important role in chronic pain, and some pain models (e.g. capsaicin induced hyperalgesia) is minimal in UV-hyperalgesia.

In summary, inflammation and hyperalgesia induced by UV-radiation – used in this study – have been thoroughly investigated and broadly accepted as a general model for inflammation and inflammatory hyperalgesia.

In conclusion – using Laser algesimetry – ibuprofen lysine salt (IbuLys) was demonstrated to be significantly superior to plain ibuprofen (Ibu) with respect to onset and duration of analgesic effect. Exploratory analysis further indicates that the analgesic onset of action of IbuLys is at about 30 min post-dose.

5. References

[1] Geisslinger, G., Menzel, S., Wissel, K. et al., Single Dose Pharmacokinetics of Different Formulations of Ibuprofen and Aspirin. Drug. Invest. **5**, 238 (1993)

[2] Hoffmann, R. T., Schmelz, M., Time course of UVA-and UVB-induced inflammation and hyperalgesia in human skin. Eur. J. Pain **3**, 131 (1999)

[3] Schaffler, K., Seibel, K., Thomsen, M. et al., Effect of acute and subchronic ReN 1869 on capsaicin-induced hyperalgesia in human skin – a study utilising somatosensory evoked potentials induced by a CO_2 Laser. Drug Res. **54**, 187 (2004)

[4] Schüler, P., Seibel, K., Chevts, V. et al., Analgetische Wirkung des selektiven Noradrenalin-Wiederaufnahmehemmers Reboxetin – Objektive und subjektive Messung. Nervenarzt **73**, 149 (2002)

[5] Schaffler, K., Medert, G., The analgesic, anti-inflammatory profile of dexketoprofen trometamol (vs. Tramadol). Der Schmerz **12**, 69 (1988); Deutscher Schmerzkongress, Düsseldorf, October 14–18, 1988

[6] Gresham, A., Masferrer, J., Chen, X. et al., Increased synthesis of high-molecular-weight $cPLA_2$ mediates early UV-induced PGE_2 in human skin. Am. J. Physiol. **270**, C1037 (1996)

[7] Levine, J. D., Reichling, D. B., Peripheral mechanisms of inflammatory pain. Textbook of Pain, 4th ed., pp. 59–84, Churchill Livingstone, Edinburgh (1999)

[8] Scholzen, T., Armstrong, C. A., Bunett, N. W. et al., Neuropeptides in the skin: interactions between the neuroendocrine and the skin immune systems. Exp. Dermatol. **7**, 81 (1998)

[9] Eschenfelder, C. C., Benrath, J., Zimmermann, M. et al., Involvement of substance P in ultraviolet irradiation-induced inflammation in rat skin. Eur. J. Neurosci. **7**, 1520 (1995)

[10] Benrath, J., Eschenfelder, C., Zimmermann, M. et al., Calcitonin gene-related peptide, substance P and nitric oxide are involved in cutaneous inflammation following ultraviolet irradiation. Eur. J. Pharmacol. **293**, 87 (1995)

[11] Gillardon, F., Moll, I., Michel, S. et al., Calcitonin gene related peptide and nitric oxide are involved in ultraviolet radiation-induced immuno-suppression. Eur. J. Pharmacol. **293**, 395 (1995)

[12] Luger, T. A., Beissert, S., Schwarz, T., The epidermal cytokine network. Skin Immune System, pp. 271–310. CRC Press, Boca Raton (1997)

[13] Scholzen, T., Hartmeyer, M., Fastrich, M. et al., Ultraviolet light and interleukin 10 modulate expression of cytokines by transformed human dermal micro vascular endothelial cells (HMEC-1). J. Invest. Dermatol. **3**, 50 (1998)

[14] Kupper, T. S., Chua, A. O., Flood, P. et al., Interleukin 1 gene expression in cultured human keratinocytes is augmented by ultraviolet irradiation. J. Clin. Invest. **80**, 430 (1987)

[15] Oxholm, A., Oxholm, P., Staberg, B. et al., Immunohistological detection of interleukin 1 like molecules and tumor necrosis factor in human epidermis before and after UVB-irradiation in vivo. Brit. J. Dermatol. **118**, 369 (1988)

[16] Kumar, S., Tzimas, M. N., Griswold, E. et al., Expression of ST2, an interleukin 1 receptor homologue, is induced by proinflammatory stimuli. Biochem Biophys. Res. Commun. **235**, 474 (1997)

[17] Francischi, J. N., Lorenzetti, B. B., Ferreira, S. H., Interleukin 1 mimics the hyperalgesia induced by a factor obtained by macrophage lysis. Braz. J. Med. Biol. Res. **21**, 321 (1988)

[18] Ferreira, S. H., Lorenzetti, B. B., Bristow, A. F. et al., Interleukin 1β as a potent hyperalgesic agent antagonised by a tripeptide analogue. Nature **334**, 698 (1988)

[19] Cunha, F. Q., Poole, S., Lorenzetti, B. B. et al., The pivotal role of tumor necrosis factor alpha in the development of inflammatory hyperalgesia. Brit. J. Pharmacol. **107**, 660 (1992)

[20] Köck, A., Schwarz, T., Kirnbauer, R. et al., Human keratinocytes are a source for tumor necrosis factor alpha: Evidence for synthesis and release upon stimulation with endotoxin or ultraviolet light. J. Exp. Med. **172**, 1609 (1990)

[21] Tobin, D., Hogerlinden, M., Toftgard, R., UVB-induced association of tumor necrosis factor receptor 1 / TNF receptor-associated factor 2 mediates activation of Rel proteins. Proc. Natl. Acad. Sci. **95**, 565 (1998)

[22] Watkins, L. R., Maier, S. F., Goehler, L. E., Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain **63**, 289 (1995)

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