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Differential effects of dipyrone, ibuprofen, and paracetamol on experimentally induced pain in man

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Abstract

In a double-blind cross-over study on 22 healthy subjects the analgesic efficacies of the antipyretic analgesic drugs ibuprofen, dipyrone and paracetamol were tested against placebo using a model of experimentally induced pain. To this purpose interdigital webs were pinched repeatedly for 2 min periods. The painfulness of these stimuli was assessed by the subjects on an electronically controlled visual analogue scale at 10 sec intervals. In addition to the subjective pain ratings the stimulus induced reflex diminution of the blood flow in the stimulated hand was measured with photoplethysmography and laser Doppler flow analysis. The flare response around the stimulated area was assessed with infrared thermography. In this assay system ibuprofen and dipyrone, but not paracetamol, showed statistically significant analgesic effects by preventing hyperalgesia which is normally induced by the repeated stimulation of a skin site. This hypoalgesic effect was not related to the subjective impression of the subjects of the analgesic potency of the respective drug. Sympathetic reflex vasoconstriction was not quantitatively related to the drug induced hypoalgesia. Ibuprofen and, to a minor extent, the other antipyretic analgesic drugs also diminished the stimulus induced flare reaction around the stimulated skin sites.

Introduction

The use of experimental studies on healthy human subjects for measuring the effects of analgesic drugs is still controversial. Most of the literature on algesimetric experiments relates to opiates which induce changes of the mood of subjects besides being analgesics. Hence, analgesic effects of opiates can hardly be blindly assessed and it is often unclear whether the subjects rate analgesic effects or their mood changes.

On the other hand, in the past numerous attempts failed to prove the analgesic effects of antipyretic analgesic drugs with experimental methods in healthy human subjects. According to Beecher [1] this is to be expected since most experimental pain stimuli are too unrealistic models of clinical pain. In the terms of Melzack and Caseys [2] three dimension model of pain, the sensory dimension seems to be prominent in experimental pain, compared with the affective and evaluative dimensions being dominant in many clinical pain states.

Newer insights into the nervous apparatus mediating pain may reveal a further reason: in the course of inflammatory processes nociceptors undergo sensitization that induces spontaneous discharges and changes in their responsiveness to chemical and physical stimuli. In turn the increased nociceptor input into the central nervous system seems to induce plasticity changes in ascending pathways

[3]. Antipyretic analgesics apparently do not significantly depress nociceptor responses in healthy tissue, but may prevent or reduce sensitization at central and/or peripheral sites.
Hence, algesimetric techniques for the study of effects of antipyretic analgesics should involve sensitization of nociceptors.
Our group has successfully employed tonic pinching of skin folds for pain induction in several studies on acetylsalicylic acid [4, 5]. When repeatedly pinching interdigital webs we found that this analgesic drug mainly depressed the increasing painfulness of repeated stimulation [5].
The aim of the present study was twofold: (a) to extend these studies to other types of antipyretic analgesics and (b) to assess other parameters of the nociceptive response besides the pain ratings to get further information on the site of the drug action. Part of the data were presented elsewhere in preliminary form [6, 7].

Materials and methods

Medication and design of the study

The neutral capsules containing placebo, paracetamol (1000 mg), racemic ibuprofen (800 mg) and dipyrone (1000 mg), respectively, were provided by Hoechst AG (Frankfurt/Main, Germany). In a double-blind cross-over design one of the above formulations was swallowed by 22 healthy volunteers (12 males, 10 females) at the beginning of an experimental session. Venous blood samples were taken prior to and 90 min after drug intake. Plasma was stored at −30 °C until later analysis.

Analysis of drug concentrations in plasma

The pure metabolites of dipyrone, 4-methylaminoantipyrine (MAA), 4-aminoantipyrine (AA), 4-formylaminoantipyrine (FAA) and 4-acetylaminoantipyrine (AAA) were kindly provided by Hoechst AG (Frankfurt/Main, Germany). R- and S-ibuprofen (99% pure enantiomers) were gifts from PAZ Arzneimittelentwicklungsgesellschaft mbH (Frankfurt/Main, Germany). Paracetamol as an analytical standard substance was obtained from Sigma Chemie (Deisenhofen, Germany). All other chemicals and organic solvents were of HPLC or reagent grade. Published high-performance liquid chromatographic (HPLC) methods were used to determine the plasma concentrations of MAA, AA, FAA and AAA [8], ibuprofen enantiomers [9] as well as paracetamol [10, 11].
The following exclusion criteria were predefined: S-ibuprofen <6 μg/ml, free paracetamol <2 μg/ml, and for the two dipyrone metabolites MAA and AA combined <5 μg/ml.
According to these criteria 4 subjects had to be excluded because of low ibuprofen levels and two further ones because of low paracetamol levels. The mainly active dipyrone metabolites MAA and AA were always found in concentrations precluding inadequate absorption.

Stimulation procedure

The mechanical stimulator has been described previously [5, 12]. The interdigital webs between the 2nd and 3rd and between the 3rd and 4th fingers were alternately squeezed with constant forces at 28 mm^2 using feedback controlled forceps (see Fig. 1). The two interdigital webs were stimulated for two minute periods with different forces of 10 N and 8 N to induce two different pain levels.

Pain related variables

Throughout each stimulus the subjects rated their instantaneous pain level at 10 s intervals, following acoustic signals. Ratings were performed by moving a lever controlling the display of a visual analogue scale (VAS) on a computer screen. The end points of the scale were defined as "no pain" and "tolerance limit".
In previous studies we found that these tonic mechanical pain stimuli induced a reflex vasoconstriction in the hand maintained throughout the stimulus period [12, 13]. Since this reflex seems to be quantitatively related to the nociceptive input [13] and probably provides parameters of its spinal and/or brainstem processing, it was also assessed in the present study in three ways: (a) the photoplethysmogram (Pleth) was recorded from the volar side of the thumb of the stimulated hand [13], (b) the blood flow through the skin of that thumb was assessed in addition by laser-Doppler flowmetry (LDF) [14], and (c) the temperature changes (cooling) at the volar side of the 2nd finger were measured at 30 s intervals by the use of infrared thermography.

After the first painful pinch stimulus a flare appears around the stimulated site which may provide a measure of early inflammatory processes. It was prominent in the thermograms as a warmer area compared to the rest of the hand. This vasodilatation was assessed by subtracting the mean temperature in the erythematous area from that of a reference area at the hypothenar. This difference was corrected for initial temperature differences at the two sites.

Measurement procedures

All data apart from the thermograms were processed into a PC-AT computer via a 12 bit AD converter and stored on hard disc. In the case of the pain ratings 12 successive values were stored during each stimulus period.

The technique of Pleth measurement has been described elsewhere in detail [12]. Briefly, the output of a photoresistor bridge provides a relative measure of the skin blood flow. To maintain comparability between sessions, calibration of the impedance bridge was fixed. The pulse amplitude was computed from the maxima and minima and stored on hard disc at $1\ s^{-1}$.

A PERIMED Pf 2a unit (PERIMED, Sweden) was used for laser-Doppler flowmetry (for details see [13]). It provides a voltage output analogous to the changes of the blood flow through the superficial skin layers which was digitized and stored at $1\ s^{-1}$.

An AGEMA camera system was used for thermography (AGEMA, Sweden). The thermograms of the volar side of the stimulated hand were scanned and processed by a 80386 PC computer at a rate of $30\ s^{-1}$ using GESOTEK software (GESOTEK, Darmstadt, Germany). The raw thermograms were stored on hard disc. For extracting the variables reflecting the stimulus induced vasoconstriction and local vasodilatation, respectively, three "areas of interest" were defined which had the same size and shape for all subjects: (a) a rectangular area at the volar site of the index finger for measuring reflex vasoconstriction (about 2.5 cm^2, 210 pixels), (b) a horseshoe shaped area around the stimulus site for assessing the local hyperemia reaction (about 2.5 cm^2, 210 pixels), (c) a square area at the hypothenar for reference (about 3.2 cm^2, 265 pixels). The mean temperature in these areas of interest was computed and used for further analysis.

The CSS software package (STATSOFT, Tulsa, USA) was used for statistical analysis and SIGMAPLOT (JANDEL, Corte Madera, CA, USA) for graphic presentation.

Subjects and experimental protocol

Twenty two healthy volunteers participated in this study, 12 males and 10 females, age 24–33 years. Each subject participated in 1 practicing session and in 4 medication sessions spaced at 7–10 days. In the practicing session the same stimuli were applied as in the following medication sessions to familiarize the subjects with the procedure. The experiments were conducted in a climatized room and the ambient temperature was kept between 23 and 24 °C.

The experimental sessions started at 8.00 am with a standardized breakfast. At 9.30 the subjects took the medication in two identical capsules with 100 ml of water. Fig. 1 shows a diagram of the stimulus protocol.

The first 8-N stimulus was delivered at 10.00 am, i.e. 30 min after drug intake, then 10-N and 8-N stimuli were applied alternately at 10-min intervals; i.e. each of the two stimulated skin areas were pinched at intervals of 20 min. The last (12^{th}) stimulus was applied 140 min after swallowing the capsules. A blood sample was taken by venous puncture 90 minutes after drug intake. At the end of each medication session the subjects rated their impression on the analgesic potency of the respective drug on a VAS ("subjective analgesis potency"). These "paper and pencil" VAS ratings must not be confused with the pain ratings obtained during an experiment on an electronically controlled VAS (see above).

The subjects were informed about the purpose of the study and the nature of the drugs, but not that a placebo was included. They were told that they were free to withdraw from the experiment at any time. They received an honorarium for participating.

The study was approved by the Ethics Committee of the Medical Faculty of the University of Erlangen-Nürnberg.

Results

Drug concentrations and exclusions: According to the exclusion criteria defined in the "Methods"-

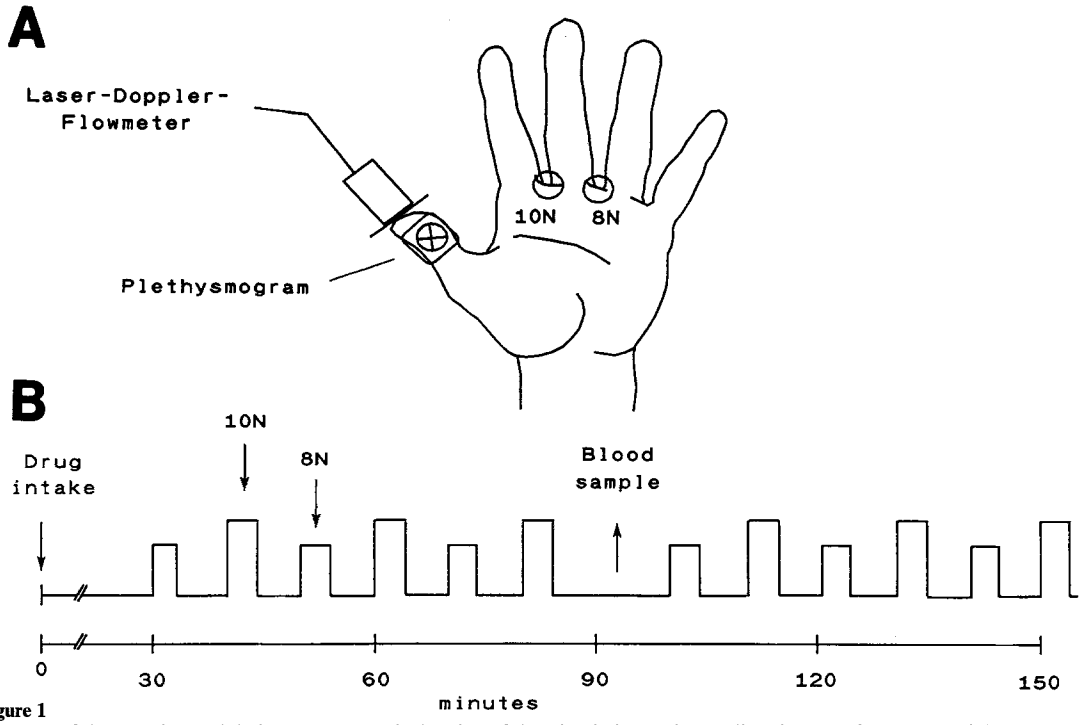

Figure 1
Diagram of the experimental design. A: Schematic drawing of the stimulation and recording sites. B: Time course of the experiment, including drug delivery, sampling of the plasma and application of the painful stimuli.

section 4 subjects had to be excluded because of low S-ibuprofen levels and 2 further ones because of low paracetamol levels. The mean ($n=22$) dipyrone metabolite concentrations measured were 9.24 ± 4.56 µg/ml; 2.29 ± 1.03 µg/ml; 0.83 ± 0.48 µg/ml and 0.29 ± 0.35 µg/ml for MAA, AA, FAA and AAA, respectively.
The mean ($n=18$) ibuprofen plasma levels were 16.54 ± 7.35 and 12.75 ± 7.32 µg/ml for S- and R-ibuprofen, respectively. The mean ($n=20$) free paracetamol concentration was 7.71 ± 2.7 µg/ml plasma.

Subjective assessments of analgesic potency

A two-way analysis of variance (ANOVA) was computed on the ratings on the analgesic potency of a medication obtained at the end of a session. The independent variables in this ANOVA were "order of the session" (3 levels) "medication" (4 levels). The ANOVA revealed a just significant effect of "medication" ($F_{3,66}=2.8, p=0.05$) whereas the effect of the "order of session" was not significant ($F_{3,66}=1.9, p=0.14$). However, the post-hoc comparisons (Scheffé-test) showed no significant differences between the drugs. The mean ratings under the different medications were in percentage of the VAS: dipyrone 18.5%, placebo 20.5%, ibuprofen 32.8%, paracetamol 36.3%. Interestingly, this order does not coincide with the order of potency in the algesimetric experiment being reversed in the case of dipyrone and paracetamol.

Effects of medication on pain ratings

Generally, the pain induced by the pinchings was described as aching and throbbing. The quality of the pain sensation did not change significantly under different medications.
As in previous studies the pain increased slowly in the course of each stimulus. Fig. 2A shows the mean time courses of the ratings throughout the 120 s stimulus periods under placebo conditions. The figure shows that the average rating level in-

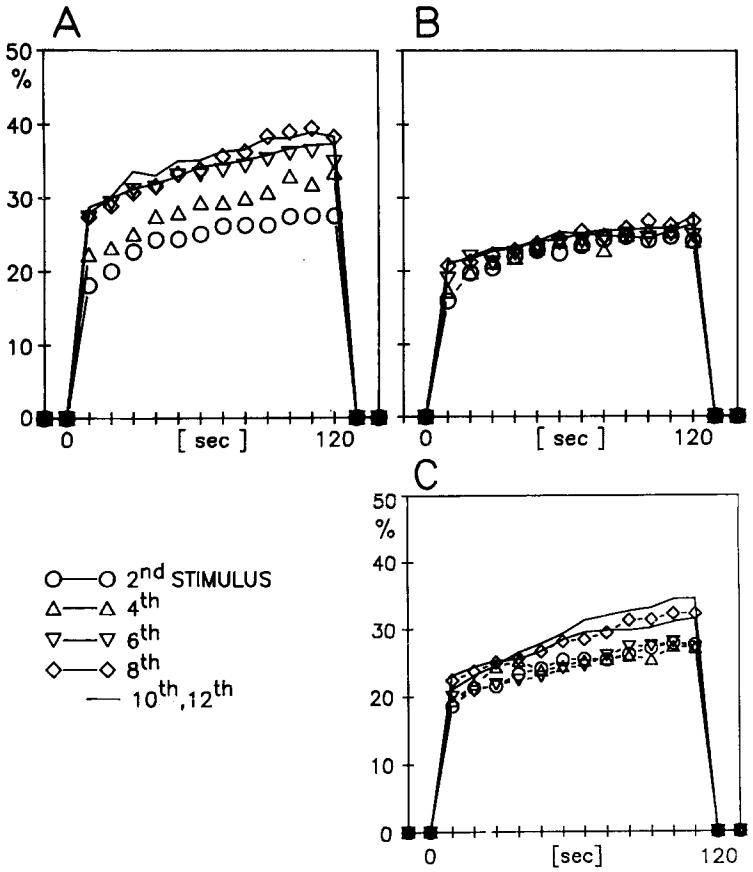

Figure 2
Time course of average pain ratings during 10 N stimuli. (A) Placebo, (B) Dipyrone, (C) Ibuprofen. The symbols represent the mean ratings given on an electronically controlled VAS during a stimulus (see method section for details).

creases during a session, but the slope of the ratings within a stimulus does not significantly change.

In the dipyrone (Fig. 2B) and ibuprofen sessions (Fig. 2C) apparently the mean rating levels do not increase as under placebo, but again the slope of the ratings within the stimuli seems to be unaltered. Therefore we used the average rating obtained during each stimulus for further statistical analysis. Fig. 3 shows the mean ratings obtained under the three analgesic medications compared to placebo.

A three-way ANOVA was computed on these data with the independent variables "medication" (4 levels), "stimulus repetition" (6 levels), and "stimulus level" (2 levels = 8 and 10 N). All factors had significant effects on the pain ratings. Medication: $F_{3,936} = 8.2$, $p < 0.01$; stimulus repetition: $F_{5,936} = 4.3$, $p < 0.01$; stimulus level: $F_{1,936} = 47.4$, $p < 0.01$). In the post hoc comparisons (Scheffé test) the following statistically significant medication effects were found: ibuprofen > placebo, dipyrone > placebo, ibuprofen > paracetamol and dipyrone > paracetamol. The effect of paracetamol was not significantly different from placebo. Dipyrone and ibuprofen had no significantly different effects.

The respective significance levels and the mean ratings under the different medications are shown in Table 1.

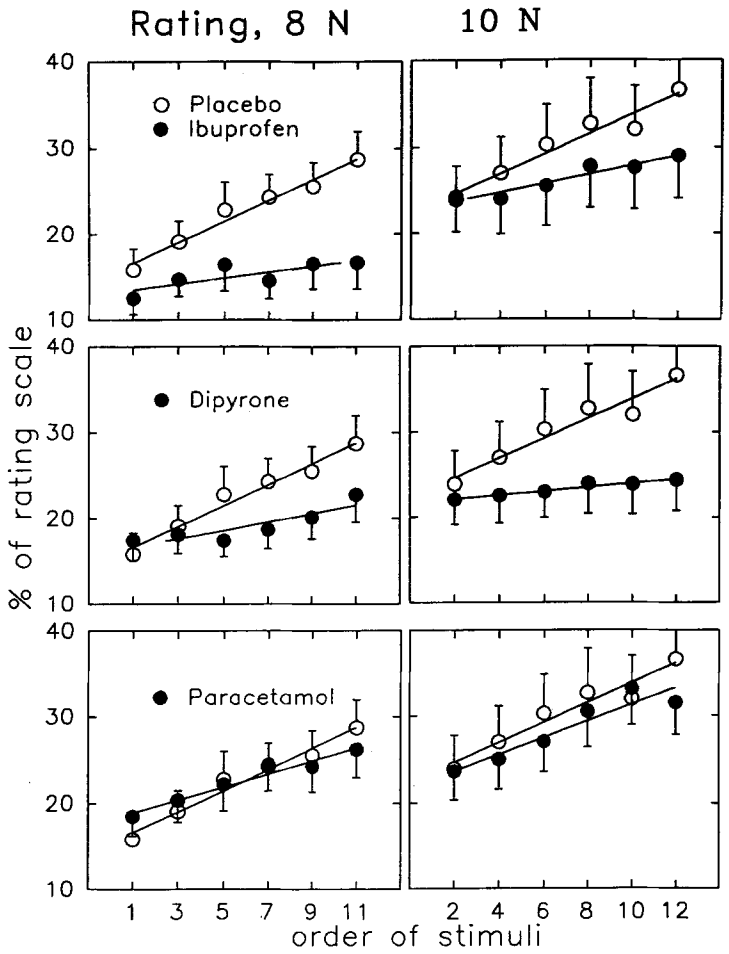

Figure 3
Mean pain ratings during the medication sessions compared with placebo. For this figure all ratings obtained during the individual 2 min stimuli are averaged. See text for the statistical significance of the differences.

Table 1
Left side: Significance levels (p) of the differences between the ratings under different medications in the Scheffé post hoc test. Right side: Grand mean of the ratings under different medications in percentage of the full rating scale.

	Para-cetamol	Ibu-profen	Di-pyrone	Rating	
				8 N	10 N
Placebo	0.95	0.002	0.006	22.1%	29.4%
Paracetamol	–	0.010	0.030	22.1%	27.8%
Ibuprofen	0.010	–	0.981	14.8%	25.5%
Dipyrone	0.030	0.981	–	18.6%	22.7%

Sympathetic reflex vasoconstriction

The decreased blood flow in the skin of the stimulated hand was measured with PLETH, LDF and from the decreases of finger temperature reflected in the thermograms. All three measures indicated slow decreases in blood flow during experimental sessions probably due to the immobilization of the hand. The reflex drops in blood flow due to the nociceptor-induced vasoconstriction were superimposed on that baseline drift (see Fig. 4). Taking the blood sample generally induced a reflex de-

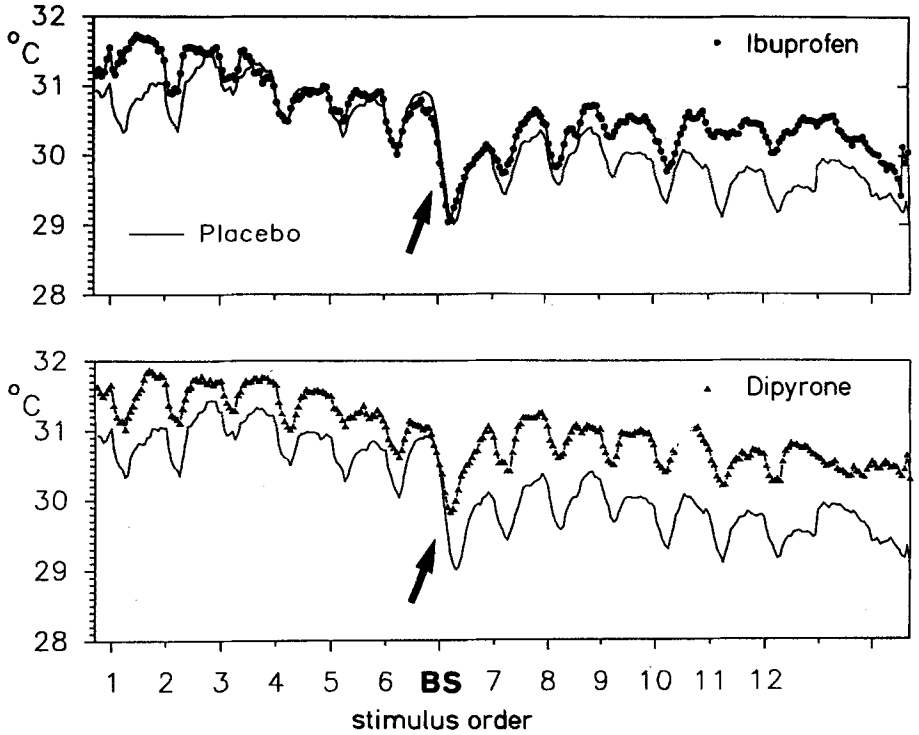

Figure 4
Average temperature changes at the volar side of the 2nd finger during the ibuprofen and dipyrone sessions compared to placebo. At the time marked by arrow (BS), a venous puncture was performed and a blood sample was taken for the assessment of plasma levels of the drugs.

crease in skin blood flow but had no significant effect on the subsequent pain ratings. However, under dipyrone the skin temperatures and PLETH-amplitudes were significantly higher than under the other medications. Average baseline temperature was 31.3 °C under dipyrone compared to 30.6 °C under placebo. Fig. 4 shows the average time courses of the skin temperatures under dipyrone and ibuprofen compared with the placebo values, respectively.

Covariance analysis of the reflex vasoconstriction (measured with PLETH, LDF or thermography) during pinch stimulation with the baseline temperature as a covariate, revealed no significant medication effects, though the covariate "baseline" had a significant effect.

Local erythema

The erythema in the surroundings of the stimulated skin sites was thermographically assessed by subtracting the mean temperature around the stimulus site from that of a reference area at the hypothenar. The temperature differences (ΔT) were corrected for the initial difference between these two sites. ΔT instead of the absolute temperatures was chosen for assessing the local reactions in order to compensate for the effects of reflex vasoconstriction affecting the whole stimulated hand. Fig. 5 shows the time courses of ΔT around the interdigital web stimulated with 8 N under ibuprofen and under dipyrone as compared to placebo.

For the statistical evaluation an ANOVA on ΔT was computed from 4 averaged thermograms obtained in the two minutes after stimulus application when this variable showed a peak. For this purpose, a four way ANOVA was computed on ΔT from both sites stimulated with 8 N and 10 N ("ΔT_{8N}" and "ΔT_{10N}") with the independent variables medication, gender, stimulus repetition and level of stimulation. All factors had a significant

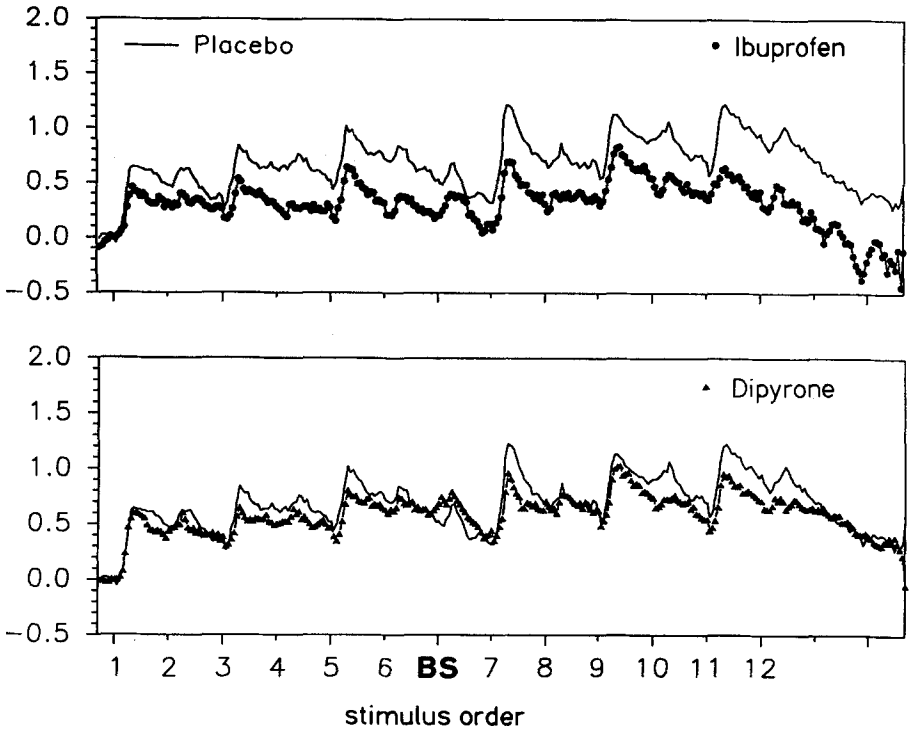

Figure 5
Average time courses of the relative warming around the stimulus site (local erythema) measured around the interdigital web which was pinched with 8 N under different medications.

Table 2
Relative warming around the two stimulated skin sites in the course of an experimental session under different medications. Temperature differences to a reference site are presented in degrees centigrade. Those values which are significantly different from those obtained in the placebo session are respectively marked.

	ΔT_{8N} (°C)	ΔT_{10N} (°C)
Placebo	0.89	0.87
Paracetamol	0.75**	0.94
Ibuprofen	0.49***	0.66***
Dipyrone	0.73**	0.77

** $p<0.01$ *** $p<0.001$ – related to placebo (Scheffé-test).

effect on both ΔT_{8N} and ΔT_{10N}. Post hoc analysis (Scheffé test) revealed the differences between the different medications shown in Table 2.

Discussion

We report a double blind cross-over study on the impact of several antipyretic analgesics on the reactions of healthy human volunteers to experimentally induced pain as compared to placebo. To our knowledge, this is the first experimental study in healthy human volunteers which proves an analgesic effect of dipyrone which apparently is in the same order of magnitude as that of ibuprofen. We had to exclude some subjects of the ibuprofen group who were found to have low plasma levels which may be due to the fact that the absorption of this drug is sometimes retardedly, especially after food intake [15].

One of the problems encountered with experimental assessment of analgesic effects is the difficulty in blindly comparing drug and placebo effects. Many analgesic drugs have side effects, from which the subjects may guess the kind of medication in a particular session. These conjectures may then influence the pain ratings. In the present study on antipyretic analgesics we tried to minimize this problem by not explicitly informing the subjects about the placebo.

Nevertheless, some subjects may have guessed the use of a placebo in one of the sessions. To assess

the possible impact of those conjectures, we asked the subjects to rate the effect of the medication at the end of each session. The ANOVA on these ratings revealed indeed a small effect of the real medication on the conjectured analgesic effect, but in the post hoc analysis we found no significant difference between real drugs and placebo. Furthermore, under paracetamol which had a negligible effect in the algesimetric tests the drug effect was rated highest whereas under dipyrone, which proved most effective in algesimetry, it was rated lowest. This may hint at a psychotropic effect of paracetamol which is apparently lacking in the other antipyretic analgesics.

Clear analgesic effects of the antipyretic analgesics were proven by the statistical analysis of the pain ratings during the pinch stimulations. Post hoc comparisons revealed that dipyrone and ibuprofen lead to significantly lower pain ratings compared to placebo, though paracetamol did not. From the data shown in Fig. 3 dipyrone was more effective in lowering the responses to the more painful 10 N stimuli; but ibuprofen was more effective in lowering the responses to 8 N stimulation. Further studies have to show if this difference is stable.

A closer look at the data shows that the ratings in response to the first stimuli in a session were not affected by dipyrone or ibuprofen, in contrast to those delivered later in a session. This probably reflects the fact that the antipyretic analgesics mainly reduced the hyperalgesia induced by repeated stimulation of a skin site. This result is in agreement to previous findings in similar experiments on acetylsalicylic acid [4, 5]. It demonstrates that antipyretic analgesics act predominantly by reducing the sensitized state of the nociceptive system. The lack of effect of paracetamol probably reflects the weak antiinflammatory action of this drug. It is compatible with the weak effects of this drug in other phlogistic pain situations [16]. Further studies are required to test whether paracetamol has perhaps a kind of mild psychotropic effect at average analgesic doses, as suggested by a study on paracetamol antipyresis in children [17].

Since we have previously shown that during noxious stimulation a sympathetic vasoconstriction occurs in the stimulated hand, we hoped to get an objective parameter of the analgesic effects by measuring the magnitude of this reaction. However, no significant differences in reflex amplitudes were found between the different medications. An interesting side effect was the increased cutaneous blood flow under dipyrone medication which may be due to the well known relaxing action of this drug on smooth muscle cells probably affecting the resistance vessels [18].

Infrared thermography was used to assess the effect of antipyretic analgesics on the flare around the stimulated area which is one aspect of the inflammatory reactions of the skin to repeated painful stimulation. We found a significant diminution of this reaction at both stimulated sites under ibuproben which seems to have the strongest antiinflammatory potency among the tested antipyretic analgesics. A weaker effect at one of both sites was also found after application of the two other drugs albeit only at the site pinched with the weaker 8 N stimulus. In the case of dipyrone this effect may have been obscured by the vasodilatory action of this agent.

The data presented in this paper show that the specific analgesic effects of antipyretic analgesics can be clearly measured in an experimental study on healthy volunteers provided the experimental model involves sensitization of the nociceptive system.

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