Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study

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Cephalalgia

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Two-hundred-and-seventy-eight patients with acute migraine attacks with or without aura were treated in 17 centers with 1.8 g lysine acetylsalicylate i.v. (Aspisol®;=1 g acetylsalicylic acid), 6 mg sumatriptan s.c. or placebo using a double-blind, double-dummy, randomized, multicenter parallel group study design. Two-hundred-and-seventy-five of them fulfilled the criteria for efficacy analysis, corresponding to 119 patients treated with lysine acetylsalicylate (L-ASA), 114 with sumatriptan and 42 with placebo injections. Both treatments were highly effective compared to placebo ($p<0.0001$) in decreasing headache from severe or moderate to mild or none (verbal rating scale, VRS, placebo=23.8%). Sumatriptan showed a significantly ($p=0.001$) better response (91.2%) compared to L-ASA (response 73.9%). Of the patients in the L-ASA-group, 43.7% were pain-free after 2 h; 76.3% after sumatriptan and 14.3% after placebo. It took patients on average 12.6 (L-ASA), 8.2 (sumatriptan), and 19.4 h (placebo) to be able to work again. There was no significant difference between treatment groups in recurrence of headache in responders within 24 h (18.2% L-ASA, 23.1% sumatriptan, 20% placebo). Accompanying symptoms (nausea, vomiting, photophobia, phonophobia, and visual disturbances) improved with both verum treatments to a similar extent. L-ASA was significantly better tolerated than sumatriptan (adverse events L-ASA 7.6%, sumatriptan 37.8%). In conclusion, subcutaneous sumatriptan and lysine acetylsalicylate i.v. are effective treatments for patients suffering from migraine attacks. Sumatriptan is more effective, but resulted in more adverse events. □

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Despite the introduction of sumatriptan and other "triptans" as an effective oral treatment for migraine, some patients are still in need of parenteral treatment for their migraine attack because of lack of efficacy, vomiting, or diarrhea. This is particularly true in the treatment of migraine attacks in emergency rooms and doctors' offices. Up until now, only subcutaneous (s.c.) sumatriptan, acetylsalicylic acid (ASA) as an i.v. lysine compound and i.v. dihydroergotamine (DHE) are available for this purpose. Subcutaneously administered sumatriptan is highly effective (1–3), but has a high frequency of adverse events. ASA administered orally in combination with antiemetics is almost as effective as oral sumatriptan (4). In contrast to the considerable clinical experience with oral ASA, only few placebo-controlled clinical studies have been performed with intravenously administered ASA in the treatment of acute migraine attacks (5, 6).

The present study was designed to compare a single dose of 6 mg s.c. sumatriptan with a single dose of 1.8 g i.v. lysine acetylsalicylate (L-ASA) in the acute treatment of migraine. The primary efficacy endpoint was the improvement of headache based on a verbal rating scale.

Patients and methods

Patients

The study was conducted in 17 centers in Germany. Patients were recruited and treated between November 1996 and January 1998. The trial was implemented in accordance with the rules and regulations of the German Drug Law, the German and European guidelines for Good Clinical Practice (GCP) and in accordance with the Principles of the Declaration of Helsinki after approval by local ethics committees. Patients (18–65 years) were eligible for the study if they met the International Headache Society (IHS) diagnostic criteria for

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migraine with or without aura (7). They were required to have a history of migraine of at least 1 year's duration and experiencing 2–6 migraine attacks per month during the last 12 months. Exclusion criteria included: participation in a study during the 30 days immediately prior to the start of the study, including the treatment of a second migraine attack, intake of analgesics, or migraine drugs 24 h before the administration of the study medication, intake of compound analgesics, sumatriptan, ergotamine tartrate, or DHE, codeine, or barbiturates on more than 10 days per month, hypertension with diastolic BP >100 mmHg and/or systolic BP >160 mmHg, coronary heart disease and/or history of myocardial infarction, asthma of any origin, hypersensitivity to salicylates, urticaria or other allergic diatheses, hypersensitivity to sumatriptan and drug intake according to DSMIIIR (alcohol, drug abuse, or dependence, also in medical history). A written informed consent was obtained.

Study design

The trial was designed as a double-blind, double-dummy, randomized, multicenter, three parallel group study of s.c. sumatriptan 6 mg, intravenous L-ASA 1.8 g (corresponding to 1 g acetylsalicylic acid), and placebo, conducted in outpatient clinics of neurology departments and offices of neurologists and pain specialists. At the time when the study was planned, some ethics committees in Germany objected to the use of placebos in migraine trials. Therefore a ratio between placebo and active treatment of 1:6 was determined. One migraine attack with moderate or severe headache, grade 2–3 on a 4-point headache severity scale (3=severe, 2=moderate, 1=mild, 0=no pain) was treated and evaluated. Patients who experienced a migraine attack with the respective pain intensity were asked to come to the relevant study center within a period of no more than 6 h after the onset of the attack. All patients qualifying under the diagnostic migraine criteria as defined by the IHS and under the inclusion and exclusion criteria were given their random numbers consecutively and in ascending order. Following the patient's information and declaration of consent, the pre-examination of patients was performed and the migraine attack documented in detail, including date and onset of attack, pain intensity according to a verbal rating scale (VRS), and a visual analog scale (VAS), autonomic accompanying symptoms, as well as measurements of heart rate and blood pressure, ECG, and blood sample collection for routine laboratory tests. The investigator then administered the investigational drugs under double-blind conditions as an i.v. and s.c. injection. The change in pain intensity was measured at 30-min intervals on a VRS and at 15-min intervals on a VAS over 120 min. Accompanying symptoms (nausea, vomiting, photophobia, phonophobia, visual disturbances) were documented at 30-min intervals (present–not present) over the 2-h observation period. Measurements of heart rate and blood pressure were performed every hour.

Recurrence of headache, defined as improvement of headache to mild or no pain after 2 h and deterioration to moderate or severe headache within 24 h, additional analgesic treatment (rescue medication), the period between the therapy with study medication and the patient's ability to resume work or usual activities—even to a limited extent—was also documented 2 h after treatment up to 48 h. In addition, adverse events were documented over 48 h after administration of study medication.

Evaluation of efficacy and safety

The primary efficacy analysis was based on the number of patients with headache relief from grade 3 or 2 to grade 1 or 0 on a VRS 2 h after administration of L-ASA, sumatriptan, or placebo. Secondary endpoints were defined as: change in the intensity of headache 2 h after administration of L-ASA, sumatriptan, or placebo measured on a VAS. The responder criterion for VAS measurements was defined as a reduction in pain intensity of at least 50%. VAS measured pain intensity was assessed before the administration of study medication and repeated at 15-min intervals up to 120 min using a new VAS form for every assessment. Further secondary endpoints were: number of patients who were pain-free (grade 0) 2 h after administration of study medication, recurrence of headache (grade 2 or 3) within 24 h after administration in those patients who experienced a reduction in pain to grade 0 or grade 1 after 2 h, rescue medication after 2 h after administration of the study medication, change in migraine accompanying symptoms 2 h after administration (nausea, vomiting, phonophobia, photophobia, and visual disturbances). Changes were documented at 30-min intervals and were classified as "not existent" (baseline: absent; 120 min: absent), "resolved" (baseline: present; 120 min: absent), "unchanged" (baseline: present; 120 min: present), and "worsened" (baseline: absent, 120 min: present). Time between administration of the study medication and patient's ability to resume work or usual activities was documented in a patient diary. Patients were monitored for adverse events continuously over 2 h after administration of the study medication. For the next 48 h, patients documented adverse events in their diary cards.

Table 1. Characteristics of patients.

Parameters	L-ASA			Sumatriptan			Placebo			Statistical analysis	
	n	Mean	s.d.	*n*	Mean	s.d.	*n*	Mean	s.d.	p_2	p_3
Age (years)	119	41.5	11.8	114	40.9	11.0	42	39.8	11.7	0.6	0.7
Height (cm)	119	169.8	7.4	114	169.3	7.0	42	169.5	8.3	0.9	0.8
Weight (kg)	119	69.2	10.9	114	69.0	12.2	42	67.2	9.9	0.7	0.7
Male sex (%)	24 (20.2)			21 (18.4)			10 (23.8)			0.7	0.8
Migraine history											
Days with headache per month	119	4.1	2.6	114	4.0	3.5	42	4.1	2.2	0.3	0.5
Migraine since (years)	119	20.4	11.5	114	19.1	11.8	42	18.3	16.0	0.3	0.2
Rate of aura (%)	119	24.2	34.9	114	30.5	39.3	42	20.0	29.9	0.2	0.2
Mean duration of attacks (h)	119	32.5	24.2	114	30.8	22.6	42	31.9	25.5	0.5	0.8

p_2 = result of comparison of treatment groups 1, 2.
p_3 = result of comparison of all three treatment groups.

Sample size and statistical analysis

Sample size calculation was based on assumed response rates (VRS) of 75% (sumatriptan), 55–75% (L-ASA) and 25% (placebo). In order to detect a significant difference (primary efficacy criterion) between 55% and 75% ($\alpha = 0.05$, $\beta = 0.2$), the number of patients required for the comparison of the active treatments was 98 patients for each treatment, i.e., a total of 196 valid patients. Based on earlier studies, a difference of 25–50% was defined as the minimum difference compared to placebo. The same conditions were used for the explorative test as for the primary target variable ($\alpha = 0.05$, $\beta = 0.2$). This allows inclusion of three times more patients in the two active treatment arms compared to placebo. The ratio between placebo and active treatment was therefore 1:6. The required minimum number of patients treated with placebo amounted to 32, i.e., at least 228 valid patients were required. Assuming a drop-out rate of approximately 10%, the final study size had to include a minimum of 252 patients.

The primary efficacy variable (response on the VRS scale) was analyzed using the χ^2 test or, if necessary, Fisher's exact test. Categorical secondary efficacy variables were tested using χ^2 tests. Continuous secondary efficacy variables were analyzed with nonparametric tests (Mann Whitney and Kruskal Wallis). All secondary variable tests were considered exploratively. Statistical analysis was based on a 5% probability for type I error. In the event of significant differences, the limit probability p was specified.

Results

Study population

A total of 279 migraine patients entered the study and were assigned to the three treatment groups. One patient dropped out prior to the start of study treatment. All of the remaining 278 patients received study medication. They constitute the group of subjects valid for the analysis of safety, and were also used as the intention-to-treat group for primary efficacy evaluation.

Three patients had to be withdrawn from the valid case collective due to violation of exclusion criteria. There were thus 275 valid cases to be analyzed for efficacy, comprising 119 patients treated with L-ASA, 114 with sumatriptan, and 42 with placebo injections.

The treatment groups were comparable in demographic characteristics of the attacks (Table 1) and also for pretreatment characteristics of the treated migraine attacks (Table 2).

Primary efficacy variable. The main result of this study was the significant difference ($p = 0.001$, Table 3) in efficacy, expressed as headache relief

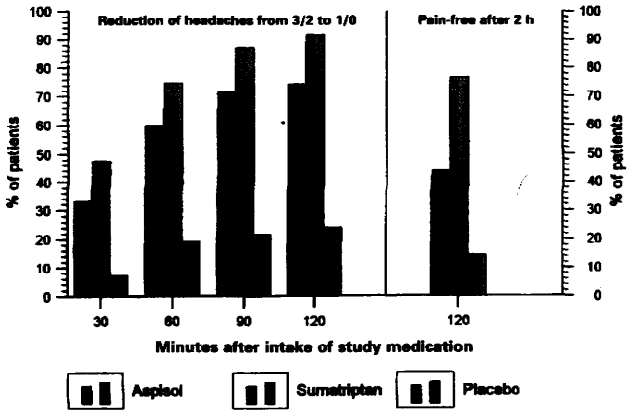

Fig. 1. Time course of reduction of headache from severe (3) or moderate (2) to mild (1) or no pain (0) after treatment with acetylsalicylic acid (left columns), sumatriptan (middle columns), or placebo (right columns). The right part of the figure shows the percentage of headache-free patients after 2 h.

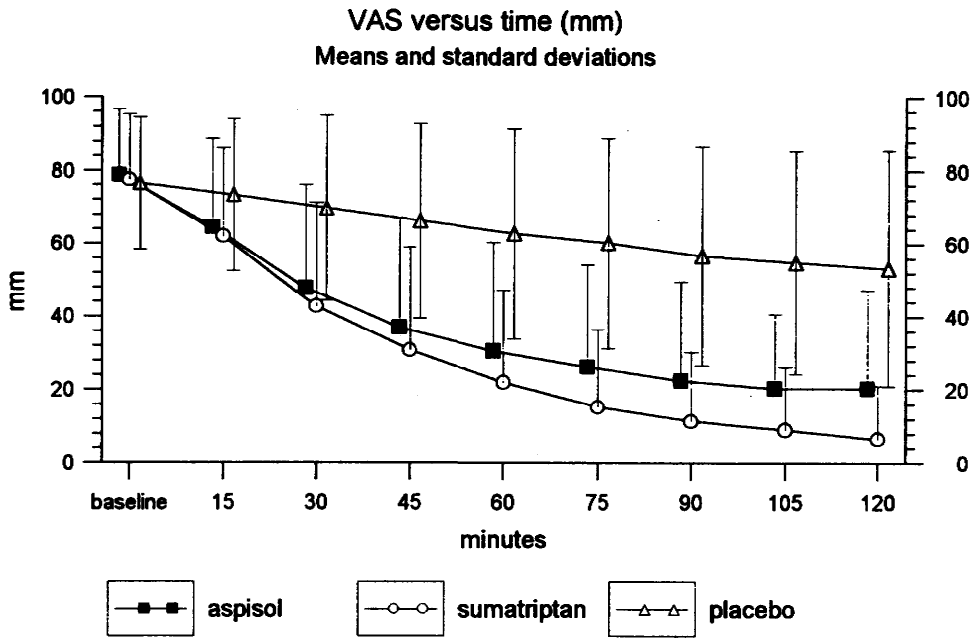

Fig. 2. Change of pain intensity measured by visual analog scale at baseline and up to 120 min after treatment with acetylsalicylic acid, sumatriptan, or placebo.

Table 2. Characteristics of treated migraine attack.

Parameters	L-ASA ($n=119$)		Sumatriptan ($n=114$)		Placebo ($n=42$)		Statistical analysis	
	No.	%	No.	%	No.	%	p_2	p_3
Aura	38	31.9	42	36.8	11	26.2	0.4	0.4
Nausea	99	83.2	99	86.8	34	81.0	0.4	0.6
Vomiting	53	44.5	56	49.1	19	45.2	0.5	0.8
Photophobia	103	86.6	97	85.1	36	85.7	0.7	0.9
Phonophobia	95	79.8	93	81.6	29	69.0	0.7	0.2
Visual disturbances	48	40.3	44	38.6	16	38.1	0.8	0.9
Other symptoms	12	10.1	13	11.5	4	9.5	0.7	0.9

p_2 = test result of comparison of treatment groups 1, 2.
p_3 = test result of comparison of all treatment groups.

Table 3. Efficacy parameters.

	L-ASA		Sumatriptan		Placebo		Statistical analysis	
	$n=119$	%	$n=114$	%	$n=42$	%	p_2	p_3
Primary efficacy parameter								
VRS-response 3/2 to 1/0	88	73.9	104	91.2	10	23.8	0.001	<0.0001
Secondary efficacy parameters								
VAS-response responder	90	75.6	108	94.7	12	28.6	<0.0001	<0.0001
Pain free after 2 h	52	43.7	87	76.3	6	14.3	<0.0001	<0.0001
Recurrence of headache within 24 h	16	18.2	24	23.1	2	20.0	0.4	0.7
Need of rescue medication	5	4.2	2	1.8	7	16.7	0.4	0.001

p_2 result of comparison of treatment groups 1, 2.
p_3 result of comparison of all treatment groups.

Table 4. Efficacy parameter, part II.

	L-ASA		Sumatriptan		Placebo		Statistical analysis	
	$n=119$	%	$n=114$	%	$n=42$	%	p_2	p_3
Nausea								
Not existing	27	22.7	17	14.9	7	16.7		
Resolved	77	64.7	86	75.4	12	28.6	0.2	<0.0001
Unchanged	15	12.6	11	9.6	21	50.0		
Worsened	0	0.0	0	0.0	2	4.8		
Vomiting								
Not existing	99	83.2	95	83.3	36	85.7		
Resolved	20	16.8	18	15.8	5	11.9	0.8	0.6
Unchanged	0	0.0	1	0.9	1	2.4		
Photophobia								
Not existing	17	14.3	20	17.5	6	14.3		
Resolved	79	66.4	82	71.9	15	35.7	0.2	<0.000.1
Unchanged	23	19.3	12	10.5	21	50.0		
Phonophobia								
Not existing	28	23.5	28	24.6	14	33.3		
Resolved	73	61.3	74	64.9	12	28.6		<0.0001
Unchanged	18	15.1	12	10.5	16	38.1	0.6	
Visual disturbances								
Not existing	83	69.7	77	67.5	31	73.8		
Resolved	34	28.6	36	31.6	2	4.8	0.7	<0.0001
Unchanged	2	1.7	1	0.9	9	21.4		

p_2 result of comparison of treatment groups 1, 2.
p_3 result of comparison of all treatment groups.

from grade 3 or 2 to grade 1 or 0, within 2 h after administration of L-ASA and sumatriptan compared to placebo (Fig. 1). Placebo was significantly inferior to both verum drugs ($p<0.0001$). Response rates after 2 h were 73.9% (88/119) for L-ASA, 91.2% (104/114) for sumatriptan, and 23.8% for placebo. The main analysis was recalculated with the intention-to-treat population instead of valid cases. The results were identical.

Secondary efficacy variables. The change in recorded mean VAS related to time is presented in Fig. 2. The study protocol defined a patient with a pain reduction of at least 50% on the VAS as responder. L-ASA (response rate 75.6%) was significantly ($p<0.0001$) less effective than sumatriptan (response rate 94.7%), but far more effective than placebo (response rate 28.6%), resulting in an overall significant difference ($p<0.0001$) for the comparison of all three groups (Table 3).

Pain-free (grade 0 of VRS) 2 h after treatment were 43.7% of the patients treated with L-ASA, 76.3% after sumatriptan, and 14.3% after placebo ($p<0.0001$). There was no significant difference with respect to recurrence of headache within the first 24 h after treatment between all three treatment groups ($p=0.7$). The L-ASA group had a recurrence rate of 18.2%, which was slightly lower than that of sumatriptan (23.1%) and the placebo rate of 20.0%. The recurrence rate after placebo has to be discussed with great caution, since only responders can have a recurrence and response rates were very low for placebo.

Rescue medication was required in 4.2% of the patients of the L-ASA group and in 1.8% of the sumatriptan group summing up to 7 patients. The corresponding number of patients was 7 for the placebo group, which results in a rescue medication rate of 16.7% for that group. This difference is significant comparing all three groups ($p=0.001$),

Table 5. Time until ability to work (h).

	L-ASA	Sumatriptan	Placebo	Statistical analysis	
n	119	114	42	p_2	p_3
Median	4.50	3.00	6.13		
Mean	12.58	8.22	19.40	0.009	<0.0001
Standard dev.	16.17	11.83	19.80		

p_2 = test result of comparison of treatment groups 1, 2.
p_3 = test result of comparison of all treatment groups.

Table 6. Migraine symptoms versus response.

Symptoms (migraine history)	Response (VRS)						Statistics
	L-ASA			Sumatriptan			
	n	Responder	%	*n*	Responder	%	*p*
With aura	38	32	84.2	42	38	90.5	0.5
Without aura	94	66	70.2	80	73	91.3	0.001
With nausea	99	77	77.8	99	90	90.9	0.01
Without nausea	20	11	55.0	15	14	93.3	0.02
With vomiting	53	45	84.9	56	52	92.9	0.2
Without vomiting	66	43	65.2	58	52	89.7	0.001
With photophobia	103	80	77.7	97	89	91.8	0.006
Without photophobia	16	8	50.0	17	15	88.2	0.3
With phonophobia	95	72	75.8	93	87	93.5	0.001
Without phonophobia	24	16	66.7	21	17	81.0	0.3
With visual disturbance	48	41	85.4	44	40	90.9	0.4
Without visual disturbance	71	47	66.2	70	64	91.4	<0.0001

Table 7. Patients with adverse events.

Patients affected by	L-ASA		Sumatriptan		Placebo		Test results	
	n=119	%	*n*=116	%	*n*=43	%	p_2	p_3
Adverse events	9	7.6	38	32.8	4	9.3	<0.0001	<0.0001
Adverse event probably related to test drug	2	1.7	17	14.7	1	2.3	<0.0001	<0.0001

p_2 test result of comparison of treatment groups 1, 2.
p_3 test result of comparison of all treatment groups.

Table 8. Adverse events—incidences related to patients per treatment group.

	L-ASA (*n*=119)		Sumatriptan (*n*=116)		Placebo (*n*=43)		Total (*n*=278)	
	n	%	*n*	%	*n*	%	*n*	%
Event grouped								
Tiredness/weariness/fatigue	4	3.3	15	12.9	1	2.3	20	7.1
Dizziness/vertigo	1	0.8	8	6.8	1	2.3	10	3.5
Nausea	4	3.3	5	4.3	0	0.0	9	3.2
Injection site reactions	0	0.0	7	6.0	0	0.0	7	2.5
Chest symptoms (tightness/pressure)	0	0.0	4	3.4	1	2.3	5	1.7
Tight feeling in various parts of the body except chest	0	0.0	3	2.5	0	0.0	3	1.0
Other	6	5.0	25	21.5	1	2.3	32	11.5

but treatments with L-ASA and sumatriptan do not differ significantly with respect to rescue medication requirement ($p=0.4$).

The changes in accompanying symptoms (Table 4) showed no significant differences between L-ASA and sumatriptan, but relief of the symptoms nausea, photophobia, phonophobia, and visual disturbances was different between verum and placebo ($p<0.0001$).

The time (in hours) between administration of study medication and the patient's ability to resume work or usual activities is given in Table 5. The mean time to working ability was 8.2 h after treatment with sumatriptan. L-ASA treated patients needed roughly 4.5 h more to be able to start their work or usual activity again (mean of 12.6 h) and placebo patients far more than twice that time (mean of 19.4 h). The differences between verum treatments ($p=0.009$) as well as between all three groups ($p<0.0001$) were significant using the Mann Whitney or Kruskal Wallis test.

Additional exploraratory analyses on reponders were performed when it became obvious that verum treatments differed substantially in efficacy with respect to accompanying symtoms (Table 6). L-ASA was more effective when accompanying migraine symptoms were present. Sumatriptan

efficacy was not dependent on the presence or absence of these symptoms. This could be an indicator of a more specific efficacy of L-ASA injections in patients showing the entire picture of migraine including accompanying symptoms. An alternative explanation is the high efficacy of sumatriptan, leading to a ceiling effect with respect to the analysis of variables which could influence the result.

Safety

Based on the intention-to-treat population (278 patients), one or more adverse events were reported by 7.6% ($n=9$) of the L-ASA-treated, 32.8% ($n=38$) of the sumatriptan-treated, and 9.3% ($n=4$) of the placebo-treated patients. The difference was significant comparing L-ASA and sumatriptan as well as in comparison of all three groups ($p<0.0001$ each; Table 7). Adverse events probably related to study drug occurred in 14.7% after sumatriptan, 1.7% after L-ASA, and 2.3% after placebo treatment ($p<0.0001$). A total of 86 adverse events was documented (Table 8), mostly weakness or tiredness of various kinds ($n=4$ L-ASA, $n=15$ sumatriptan, $n=1$ placebo). Dizziness and nausea were next frequent ($n=5$ L-ASA, $n=13$ sumatriptan, $n=1$ placebo). Chest symptoms, which are most specific for the sumatriptan group, were reported 5 times (4 events in the sumatriptan group, one in the placebo group). Injection site reactions were only reported in the sumatriptan group. A total of 36 events have been classified as "mild" another 40 as "moderate"; 11 events were assessed "severe" ($n=4$ L-ASA, $n=6$ sumatriptan, $n=1$ placebo).

Discussion

This study demonstrated in a large group of patients with severe migraine attacks in a placebo-controlled, multicenter study by direct comparison that acetylsalicylic acid and sumatriptan show a high rate of therapeutic success when used parenterally; 91% of the patients receiving sumatriptan and approximately 75% of the patients treated with L-ASA showed a positive headache response (VRS from grade 3/2 to grade 1/0) 2 h after administration. Similar results were obtained when a VAS was used. Response rates are much higher compared to oral treatment with sumatriptan or acetylsalicylic acid (4, 8). The data on treatment responses for sumatriptan and placebo are consistent with those obtained in other studies (3). It can therefore be excluded that differences in efficacy between treatment groups were influenced by differences between the treatment groups with respect to demographic and prognostic parameters (history of migraine, severity of migraine attacks, accompanying symptoms, concomitant illnesses, concomitant treatments, etc.). Although obtained in a multicenter study, the data collected with respect to these parameters were homogeneous between the treatment centers and treatment groups.

At the same time, however, the results obtained in this study also show significant differences in the efficacy of L-ASA and sumatriptan with respect to most of the secondary target variables. Sumatriptan achieves a higher rate of headache-free patients after 2 h. The higher efficacy of sumatriptan, however, was associated with a significantly higher incidence of adverse events. Adverse events were documented for a third of the sumatriptan population, while this was the case in only 8% in the L-ASA and 9% in the placebo group. In relation to the size of the investigated population, adverse events such as tiredness (incidence 13%), nausea and vertigo (11%), skin reactions at the injection site (6%), and feeling of tightness in the chest (3%) in the sumatriptan group have to be compared with incidence rates such as tiredness (3%), nausea and vertigo (4%) in the L-ASA group. This result is interesting in a different aspect: until now it has not been clear whether tiredness, dizziness, and nausea are side effects of sumatriptan or whether they reflect a change in perception, when the headache has improved due to treatment. This study, however, showed that these events are very rare after L-ASA despite a comparable treatment effect and therefore must be due to sumatriptan itself. In the emergency room situation L-ASA has another advantage: L-ASA can be given to patients with vascular contraindications for sumatriptan.

This study investigated whether use of the verbal rating scale introduced by Glaxo gives similar results compared to a VAS. VASs are used in studies of other pains. Our study shows that both methods procured identical results.

In an effort to find further decisive criteria for the use of these two parenterally effective migraine substances that go beyond practicability (s.c. or intravenous formulation) and cost considerations the collected data were further stratified and analyzed exploratively. There were no differences in the efficacy of the two antimigraine drugs in patients with aura, vomiting, and visual disturbances during the migraine attack. These interesting results are at least considered to be essential for the planning of further studies of migraine with L-ASA.

In summary, s.c. sumatriptan and i.v. aspirin are highly effective drugs in the treatment of acute migraine attacks in the setting of an emergency room or doctor's office. Sumatriptan is more effective, but has more side effects and is more

expensive. The use of rating scales ("Glaxo-scale") gives similar results as those obtained with VASs.

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