Intravenous, intramuscular and subcutaneous treatments

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Bell et al, 1990[70] **Study design:** RCT – single blind **Comparison:** 3 arms: Antiemetic (chlorpromazine) vs lidocaine vs ergot (dihydroergotamine) **Setting:** 2 university affiliated emergency departments **Duration of follow-up:** 24 hours	**Patient group:** Adults (18-60yrs) presenting to emergency department with migraine. **Inclusion criteria:** Migraine diagnosed by emergency physician defined as either: 'common' characterised by recurrent attacks of headache lasting hours or days, associated with gastrointestinal disturbance, and having some features of pulsatile character, photophobia, sonophobia, unilaterality, and positive family history; or 'classic' exhibiting recurrent attacks of headache as in common migraine but preceded by a motor, sensory or visual aura. **Exclusion criteria:** Non-migraine headache, aged under 18 or over 60, substance abuse, neurologic or seizure disorder, alcohol abuse, allergy or sensitivity, pregnancy or breast feeding, peripheral vascular disease, coronary vascular disease, hypertension, or hepatic or renal failure. **All patients** **N:** 90 (76 completed) **Age (mean):** NR	**Group 1:** 12.5mg chlorpromazine IV **Group 2:** 1mg dihydroergotamine (DHE) IV **Group 3:** 50mg lidocaine IV All patients had an IV line started and received a 500ml bolus of normal saline, followed by the study drug. The initial dosage could be repeated once at 30 minutes for a total max dose of 2mg DHE, twice at 20min intervals for total max dose of 37.5mg chlorpromazine and twice at 20min intervals for total max dose of 150mg lidocaine. IV drip of normal saline maintained during therapy at 75ml/hr. If patient didn't respond or deteriorated, physician could terminate study and use alternative therapy.	**Pain free up to 2 hours** * reported as complete relief at 1 hour (n (%)) **Remaining pain free at 24hrs** N (%) NB. N values too low	**Group1:** 8/24 (33.3) **Group 2:** 6/26 (23.1) **Group 3:** 2/26 (7.7) **95% CI:** NR **p value:** NS **Group1**: 16/18 (88.9) **Group 2:** 10/19 (52.6) **Group 3:** 5/17 (29.4) **95% CI:** NR **p value:** NR	**Funding:** Not stated **Limitations:** N values very low. Single blind (patients only). Groups not comparable at baseline. 14 patients dropped out after randomisation but the numbers are not given by group. Not clear how many patients had additional study drug doses. Analysis not clear. High risk of bias. **Additional outcomes:** Headache severity on a 10cm VAS. Additional medication taken in following 24 hours (narcotics or chlorpromazine). Patients opinion on medication received. **Notes:** States that analysis showed the three groups were

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	M/F: 16/60 44% history of migraine 43% family history (42% both) **Drop outs:** 19 (either due to incomplete records, early self-discharge or request for withdrawal from the trial) **Group 1 – Chlorpromazine** **N:** 24 **Age (mean):** NR for any group **Drop outs:** NR for any group **Headache intensity (0-10 mean):** 8.5 **Group 2 - Dihydroergotamine** **N: 26** **Headache intensity (0-10 mean):** 7.5 **Group 3 - Lidocaine** **N: 26** **Headache intensity (0-10 mean):** 8.0				statistically different, assumed this was at baseline). Groups 2 and 3 were subsequently found not to differ (except for side effects) and therefore were grouped for comparisons to group 1. Dosage could be repeated after 30 mins, therefore cannot be sure pain free was at 1 hour, but it would still be within a 2 hour window.

Abbreviations: NR=not reported, NS=not significant, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IV=intravenous, DHE=dihydroergotamine

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Brousseau et al, 2004[110] **Study design:** RCT **Comparison:** Antiemetic (Prochlorperazine) vs NSAID (Ketorolac) **Setting:** 2 Paediatric emergency departments (ED) **Duration of follow-up:** 48 hours	**Patient group:** Children aged 5-18 (avg 13) presenting to emergency department with migraine. **Inclusion criteria:** Aged 5-18 meeting Prensky and Sommer criteria for migraine: Recurrent headaches with pain-free intervals and at least 3 of the following: 1) an aura; 2) unilateral location; 3) throbbing pulsatile pain; 4) nausea, vomiting or abdominal pain; 5) relief after sleep; and 6) a family history of migraines. **Exclusion criteria:** Any contraindications to the use of either Prochlorperazine or ketorolac and those unable to complete a Nine Faces Pain Scale. **All patients** **N:** 62 (36 F) **Age (mean):** 13.7 (7.25-18) **Group 1 – Prochlorperazine** **N:** 33 (18 F, 15 M) **Age (mean (SD)):** 13.8 (3.0) **Initial pain score (SD) max 1:** 0.82 (0.11)	**Group 1** - IV Prochlorperazine (0.15mg/kg; max 10mg) **Group 2** – IV ketorolac (0.5mg/kg; max 30mg) Both administered over a 10 min period. Each child, concurrent with study medication, received a 10mL/kg bolus of normal saline solution over a 30-minute period to standardize treatment protocol. If initial treatment not successful, the child received the other medication (again blinded). Pain scoring repeated. All children discharged with a prescription for naproxen sodium (5mg/kg) 3 times per day for 48 hours as needed for pain.	**Pain free up to 2hrs** Lowest possible pain score after 60mins (% (n))	**Group1:** 33.3% (11/33) **Group 2:** 6.9% (2/29) **95% CI:** 8-45%	**Funding:** No outside funding or support **Limitations:** Age range might make population inappropriate. Pain scale doesn't meet our criteria for 'headache response' **Additional outcomes:** Treatment success defined as a ≥50% reduction in pain score (30 or 60 min after drug) Taken from Nine Faces Pain Scale Headache recurrence at 48 hours Adverse events if reported **Notes:** Block randomised by hospital pharmacist who held code for blinding until study completion. Only randomised once decision had been made to treat with IV medication.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Previous clinical diagnosis of migraine %: 61 **Current migraine duration (hr, median):** 25 **Use of migraine specific medication pre ED visit %:** 32 **Any pain medication pre visit:** 84.8 **Drop outs:** 1 (after 60 minutes) **Group 2 - Ketorolac** **N:** 29 (18 F, 11 M) **Age (mean (SD)):** 13.7 (2.6) **Initial pain score (mean (SD)) max 1:** 0.82 (0.08) **Previous clinical diagnosis of migraine %:** 55 **Current migraine duration (hr, median):** 24 **Use of migraine specific medication pre ED visit %:** 35 **Any pain medication pre visit:** 82.8 **Drop outs:** 1 (after 60 minutes)				

Abbreviations: NR=not reported, NS=not significant, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, ED=emergency department, IV=intravenous

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diener, 1999[210] **Study design:** Multicentre RCT **Comparison:** Triptan v aspirin **Setting:** 17 centres in Germany **Duration of follow-up:** NR	**Patient group:** Adults with migraine **Inclusion criteria:** Age 18-65 years. Met IHS criteria for migraine with or without aura. History of migraine of at least 1 year's duration. Experiencing 2-6 migraine attacks per month during the last 12 months. **Exclusion criteria:** 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 hours before the administration of the study medication. Intake of compound analgesics, sumatriptan. Ergotamine tartrate or DHE, codeine or barbiturates on > 10 days per month. Hypertension with diastolic BP >160mmHg. 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). **All patients** **N:** 279 randomised 278 received study medication (ITT) **Drop outs:** 4 (1 patient unaccounted for in the randomised groups below **Group 1 (sumatriptan)**	**Group 1** Sumatriptan 6 mg (subcutaneous) **Group 2** L-ASA 1.8g (corresponding to 1g acetylsalicylic acid) (intravenous) **Group 3** Placebo injections (results not reported in this table) **All patients** Patients who experienced a qualifying migraine attack were asked to come to the study centre within a period of no more than 6hours after the onset of the attack. Change in pain intensity was measured at 30 min intervals on a VRS and at 15 min intervals on a VAS over 120 min.	**Headache response up to 2 hours**	**Group1 (sumatriptan):** 104/114 (91.2%) **Group 2 (L-ASA):** 88/119 (73.9%) **p value:** 0.001	**Funding:** Bayer Vital. GmbH % Co, KG, Germany **Limitations:** Randomisation unclear: patients were given their random numbers consecutively and in ascending order. Allocation concealment: unclear. **Additional outcomes:** Change in pain intensity measured by VAS over time (2hours). VAS response responder. Recurrence of headache within 24 hours. Time until ability to work. Need of rescue medication. Relief of accompanying symptoms. Adverse events. **Notes:** Headache severity 3= severe 2= moderate 1= mild 0= no pain
			Pain free at 2 hours	**Group1:** 87/114 (76.3%) **Group 2:** 52/119 (43.7%) **p value:** <0.0001	
			Sustained headache response at 24 hours (derived from those with recurrence of headache at 24 hours)*	**Group1**: 80/114 * **Group 2:** 72/119 * Not significant	
			Serious adverse events	**Group1:** 6 **Group 2:** 4 **p value:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 116,114 received treatment dose **Age (mean):** 40.9 (SD 11.0) **Male sex:** 21 (18.4%) **Days with headache per month:** 4.0 (SD 3.5) **Migraine since (years): 19**.1 (SD 11.8) **Rate of aura (%):** 30.5 (SD 39.3) **Mean duration of attacks (h):** 30.8 (SD 22.6) **Drop outs:** NR **Group 2 (L-ASA)** **N:** 119, 119 received treatment dose **Age (mean):** 41.5 (SD 11.8) **Male sex :**24 (20.2%) **Days with headache per month:** 4.1 (SD 2.6) **Migraine since (years):** 20.4 (SD 11.5) **Rate of aura (%):** 24.2 (SD 34.9) **Mean duration of attacks (h):** 32.5 (SD 24.2) **Drop outs:** NR **Group 3 (placebo)** **N:** 43, 42 received treatment dose **Age (mean):** 39.8 (SD 11.7) **Male sex:** 10 (23.8%) **Days with headache per month:** 4.1 (SD 2.2) **Migraine since (years):** 18.3 (SD 16.0) **Rate of aura (%):** 20.0 (SD 29.9) **Mean duration of attacks (h):** 31.9 (SD 25.5) **Drop outs:** NR				Ratio Placebo to active treatments 1:6. Blinding: double-blind, double-dummy

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society, VRS=verbal rating scale, VAS=visual analogue scale, DHE=dihydroergotamine

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Duarte et al, 1992[240] **Study design:** RCT **Comparison:** NSAID (ketorolac) vs opioid + antiemetic (meperidin + hydroxyzine) **Setting:** Emergency department (ED) **Duration of follow-up:** 1 hour / discharge from ED	**Patient group:** Adults presenting to ED with migraine with or without aura **Inclusion criteria:** Migraine with or without aura diagnosed according to ICHD criteria. **Exclusion criteria:** First migraine, allergy or sensitivity to study drugs, known intracranial masses, traumatic etiology, gastritis, peptic ulcer disease, bleeding dyscrasias, **pregnancy** and nursing mothers. **<u>All patients</u>** **N:** 49 patients enrolled, representing 52 visits. **Drop outs:** 2 withdrew before receiving medication leaving 50 cases from 47 patients for analysis) **<u>Group 1 –</u>** <u>Ketorolac</u> **N:** 25 **Age (mean±SD):** 34.9 ±10.1 **M/F (%):** 20/80 **Headache duration, hours (mean±SD):** 41.4±38.1 **Initial pain score, cm (mean±SD):** 7.74±1.84 **<u>Group 2</u>** - <u>Meperidine/Hydroxyzine</u> **N:** 25 **Age (mean):** 34.4± 12.3 **M/F (%):** 20/80 **Headache duration, hours (mean±SD):** 16.5±20.5 **Initial pain score, cm (mean±SD):** 8.28±1.65	**Group 1** Ketorolac 60mg IM injection **Group 2** Meperidin (100mg) and hydroxyzine (50mg) IM injection Patients received a single IM injection in left deltoid(arrived pre-mixed at ED by pharmacy)	**Headache response up to 2 hours** Recorded at 30 and 60 mins. 60 mins reported here. Based on verbal descriptor scale.	**Group1:** 15/25* (60%) **Group 2:** 14/25* (56%) **p value:** 0.77	**Funding:** NR **Limitations:** Patients consecutively randomised as presented in ED – 3 patients enrolled twice. No details on random number tables. N values very low. Groups different in headache duration at time of enrolment (group 1 longer). **Additional outcomes:** Pain intensity on a 10cm VAS scale at 30 and 60 minutes. Adverse events reported (but not classified for severity). Need for additional analgesia after study. **Subgroups:** Pregnant women excluded. Under 18s excluded. **Notes:** * Calculated by NCGC All patients in ketorolac group and 4 of 5 patients in meperidine/hydroxyzxine group who reported a small amount of pain relief required additional analgesia, as did all five patients from both groups who obtained no pain relief (no differences between groups).

Abbreviations: NR=not reported, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, ED=emergency department, IM=intramuscular, ICHD=International classification of headache disorders

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Friedman et al, 2005[296] **Study design:** RCT **Comparison:** Triptan vs antiemetic **Setting:** 2 emergency departments in USA **Duration of follow-up:** 24 hours	**Patient group:** Adults with migraine with or without aura **Inclusion criteria:** ≥18 years old. Migraine with or without aura as defined by the IHS **Exclusion criteria:** High likelihood that patient had secondary headache or if patient was to receive a lumbar puncture in the ED. Temperature >100.3 degrees, pregnancy, lactation, allergy to a study medication or use of a study medication within 2 days. Known or suspected atherosclerotic disease or hypertension. New objective neurologic abnormality at the time of physical exam Use of sumatriptan during the planning phase of the trial, during the current migraine attack. **All patients** **N:** 78 **Drop outs:** NR **Group 1 (sumatriptan)** **N:** 38 **Age (mean):** 34 **Gender F (%):** 84 **Migraine with aura (%):** 8	**Group 1 (sumatriptan)** 6 mg SC administration by clinical nurse. Bag also contained 4 vials of placebo which were injected into the 50mL bags of normal saline and administered IV at 30 minute intervals by the clinical nurse. Each arm B bag also contained 2 vials of placebo which were inserted into saline bags 1 and 3. **Group 2 (metoclopramide+ diphenhydramine)** IV administration. Each bag contained 4 vials, each containing 20mg of metoclopramide. The contents of each vial were inserted into a 50mL bag of normal saline by a clinical nurse. These normal saline bags containing metoclopramide were then administered IV at 30 minute intervals. In addition, each Arm A bag had 2 vials, each containing 25mg of diphenhydramine. The diphenhydramine was inserted into saline bags 1 and 3 along	**Pain-free at 2 hours**	**Group1:** 13/37* (35%) **Group 2:** 24/40* (59%) **Difference:** 24% **95% CI:** 2 to 46% **p value:** 0.04	**Funding:** NR **Limitations:** Patients with chronic migraine headache were not excluded. Patients with a past history of triptan use (14%) were not excluded. Subjects in the sumatriptan group could have had a placebo response as they received up to 4 doses of IV placebo. Substantially more patients in the metoclopramide arm had pre-medicated prior to presenting to the ED. **Additional outcomes:** Use of rescue medication. Adverse events. Early discharge due to sufficient pain relief. Comparison of the change in NRS (numerical rating scale) scores between time 0 and 2 hours. Relief of nausea. **Notes:**
			Pain free at 24 hours	**Group1:** 10/37* (27%) **Group 2:** 16/40* (40%) **Difference:**13% **95% CI:** -9 to 35% **p value:** 0.23	
			Functional health status at 2 hours	**Group1:** 26/37* (69%) **Group 2:** 34/40* (85%) **Difference:**16% **95% CI:** -3 to 35% **p value:** 0.10	
			Functional health status at 24 hours	**Group1:** 18/37* (49%) **Group 2:** 19/40* 68%) **Difference:**19% **95% CI:** -3 to 41% **p value:** 0.09	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Prophylactic medication (%): 0 **Duration of headache (95% CI), h:** 29 (22-37) **Self-medicated prior to ED visit, %:** 60 **Drop outs:** 1 **Group 2 (metoclopramide)** **N:** 40 **Age (mean):** 34 **Gender F (%):** 88 **Migraine with aura (%):** 8 **Prophylactic medication, (%):**3 **Duration of headache (95% CI) h**: 32 (26-39) **Self-medicated prior to ED visit %:** 83 **Drop outs**: 0	with the metoclopramide by the clinical nurse. Finally, each arm A bag had a vial of 'sumatriptan' placebo which was administered SC by the clinical nurse. All Patients At time 0, subjects received one SC injection (containing either placebo or sumatriptan) as well as one 50mL bag of IV normal saline (containing either metoclopramide and diphenhydramine or placebo). Every 30 minutes the research assistant would ask if the subject required more medication for headache. If so, the subject received an additional IV infusion containing either metoclopramide or placebo. The protocol lasted for 2 hours.			* numbers calculated by NCGC using percentages reported. These have been rounded to whole numbers. Pharmacist inserted medication into vials and placed the vials into sequentially numbered brown paper research bags in an order determined by random number tables. Randomisation in blocks of 6 using computer-generated random number tables. Allocation concealment: sealed opaque manila envelope. Blinding: double-dummy. Study population largely Latino.

Abbreviations: NR=not reported, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, ED=emergency department, AE=Adverse events, IV=intravenous, SC=subcutaneous, IHS=International headache society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Karabetsos et al, 1997[418] **Study design:** RCT **Comparison:** NSAID (ketoprofen) vs paracetamol **Setting:** Not stated – but all patients treated as outpatients **Duration of follow-up:** 4 hours	**Patient group:** Adults with classical or common migraine **Inclusion criteria:** Suspected acute migraine attack, Paroxysmal headache accompanied by at least two of the following: (a) unilateral pain, (b) nausea, (c) visual and/or limb symptoms and (d) positive family history. Average of at least 2 or more attacks each month, Not receiving recognized migraine prophylactic drugs or oral contraceptives. **Exclusion criteria:** History of allergy to NSAIDs, under 18 yrs of age, pregnant or lactating. **All patients** **N:** 64 **Age (mean):** 42.2 (20 – 64yrs) **Drop outs:** None **M/F:** 28/36 **Group 1 – Ketoprofen** **N:** 34 **Age (mean):** 42.2 **Migraine type:** 15 classical, 19 common **Attack frequency/month:** 1-3 **Severity of symptoms**: 1 slight, 8 moderate, 25 severe	**Group 1 Ketoprofen** IM injection 100mg If pain persisted up to 30 minutes, or if relapse occurred during first or second hour after first dose, a second dose of ketoprofen was administered. No further doses were allowed – NB results reported after the 1st dose time. **Group 2 Paracetamol** IM injection 500mg	**Time to freedom from pain** Mean, hrs (SD) **Pain free up to 2 hours** (reported at 30-40 mins) **% reporting serious AEs**	**Group1:** 4.9 (5.15) (n=24) **Group 2:** 3.6 (2.4) (n=28) **P value:** 0.909 **Group 1:** 28/34 **Group 2:** 5/30 **P value:** <0.001 **Group1:** 0 **Group 2**: 0 **p value:** Not significant	**Funding:** NR **Limitations:** Study says it was a crossover, but methods stated don't reflect this – assumed to be a parallel design. Randomisation and blinding methods not clear. Setting not stated, but possibly ED. **Additional outcomes:** Severity of headache. Severity of associated symptoms. Overall rating of the effect of drug on migraine attack. Adverse events. **Notes:** Not clear at what point results are reported, or if sample size reported for time to freedom from pain is the n that achieved freedom from pain, or n the sample was taken from.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 - Paracetamol **N:** 30 **Age (mean):** 42.4 **Migraine type:** 14 classical, 16 common **Attack frequency/month:** 1.3-3.3 **Severity of symptoms:** 1 slight, 9 moderate, 20 severe				

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, AE=adverse events, ED=emergency department, IM=intramuscular

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Karachalios et al, 1992[419] **Study design:** RCT **Comparison:** NSAID (Diclofenac sodium) vs paracetamol **Setting:** NR **Duration of follow-up:** 180mins	**Patient group:** People over 18 with acute migraine **Inclusion criteria:** Fulfill Vahlquist's criteria for migraine: paroxysmal headaches accompanied by at least two of the following: 1) unilateral pain, 2) nausea, 3) visual and limb symptoms & 4) positive family history. Average of at least 2 attacks each month. Not receiving recognised migraine prophylactic drug or oral contraceptives. **Exclusion criteria:** History of allergy to NSAID, aged under 18 or pregnant or lactating women. **All patients** **N:** 86 **Drop outs:** 2 (developed severe headache and refused second injection) **Group 1 – Diclofenac** sodium **N:** 46 **Age (mean):** 47.5 18 M, 21 F **Migraine type:** 19 Classical, 26 Common **Attacks/month (mean):** 2±1 **Symptom severity:** 1 slight, 10 moderate, 35 severe **Group 2 - Paracetamol**	**Group 1 –** Diclofenac sodium 75mg injection (Intramuscular) **Group 2 -** Paracetamol 500mg injection (Intramuscular) If pain persisted up to 30mins after injection, or if headache relapsed during first or second hour after first dose, a second dose of diclofenac was administered.	**Pain free up to 2hrs** n (%) at 30-35 minutes) **Percentage reporting serious adverse events**	**Group1:** 40/45 (88%) **Group 2:** 7/40 (17.5%) Relative risk: 95% CI: **p value:** <0.001 **Group1:** 0 **Group 2:** 0	**Funding:** NR **Limitations:** States groups were comparable at baseline except for length of migraine history, but data not reported. Two subjects withdrew, but don't know which group they were in. Setting not stated, but possibly ED. **Notes:** Five patients in diclofenac group needed another injection for complete relief of pain during 2-4 hour follow-up period. 33 paracetamol patients did not respond to drug and were treated with IM diclofenac after 30 minutes of follow-up observation (complete relief of pain observed after 30-45 minutes in 32 of these patients. Second dose of treatment allowed, but pain free still would have fallen within 2hours.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 40 **Age (mean):** 48.3 **Migraine type:** 20 Classical, 21 Common **Attacks/month (mean):** 2.5±1.1 **Symptom severity:** 1 slight, 10 moderate, 30 severe				

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society, ED=emergency department

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Touchon et al, 1996[798] **Study design:** Randomised crossover study **Comparison:** Triptan vs dihydro-ergotamine **Setting:** Outpatient **Duration of follow-up:** Not reported	**Patient group:** Migraine **Inclusion criteria:** Men and women aged 18-65, at least 1 year history of 1 to 6 migraine attacks per month, able to differentiate migraine attacks from other types of headache, IHS criteria for migraine with or without aura, usually experienced frequent and disabling migraine attacks with severe/moderate headache. **Exclusion criteria:** Lactation, pregnancy or inadequate contraception, history suggestive of ischemic heart disease, uncontrolled hypertension or other systemic disease, drug or alcohol abuse, contraindications to the use of dihydroergotamine, hypersensitivity to or intolerance of sumatriptan or dihydroergotamine. **All patients** **N:** 317, 289 treated 1st	**Group 1** 1st attack Sumatriptan & placebo DHE 2nd attack Dihydroergotamine (DHE) & placebo Sumatriptan **Group 2** 1st attack DHE & placebo Sumatriptan 2nd attack Sumatriptan & placebo DHE 2 attacks treated in each group (1 per treatment) Drugs Sumatriptan 6mg subcutaneous injection into thigh from prefilled syringe with auto injector device Dihydroergotamine (DHE) nasal spray (1 spray of 0.5mg in each nostril) Patients taking DHE had the option to take a 2nd dose after 30 minutes of 1st dose if headache not	**Headache reseponse at 2 hours** reduction of headache severity from grade 2 (moderate) or 3 (severe) at baseline to 0 (none) or 1 (mild)	Data not reported. States Sumatriptan significantly better than DHE **p value:** ≤ 0.001	**Funding:** Glaxo Wellcome **Limitations:** Details on randomisation and allocation concealment not provided. No mention of a washout period. Actual event rates not provided, calculated from percentages. Patients on DHE permitted to take a 2nd dose if inadequate headache relief, patients on Sumatriptan not permitted to take 2nd dose. **Additional outcomes:** Nausea, vomiting, photophobia & phonophobia relief at 2 hours; 'meaningful' (undefined) relief of attack, rating of treatment efficacy by patients (5 point scale); number of adverse events; patients withdrawing from study due to adverse events.
			Freedom from pain at 2 hours reduction of headache severity from grade 2 (moderate) or 3 (severe) at baseline to 0 (none)	Data not reported. States Sumatriptan significantly better than DHE **p value:** ≤ 0.001	
			Sustained headache response at 24 hours – patients with headache response at 2 hours and neither recurrence nor use of rescue medications in 24 hours.	**Sumatriptan:** 144*/266 (54%) **DHE:** 104*/266 (39%) **p values:** <0.001 * number calculated by NCGC	
			Use of rescue medication	**Sumatriptan:** 74*/266 (28%) **DHE:** 112*/266 (42%) **p values:** <0.001 * number calculated by NCGC	
			Use of 2nd dose of DHE (or placebo if using active Sumatriptan)	**Sumatriptan:** 146*/266 (55%) **DHE:** 226*/266 (85%) **p values:** <0.001	

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	attack, 266 treated 2nd attack as well **Drop outs:** 51 **Group 1** **N:** No. randomised NR, 145 treated 1st attack, 133 treated 2nd attack as well **Age (mean):** 42±10 (n=133)* **Gender F/M:** 119/14 (n=133)* **Drop outs:** NR **Usual severity of headache:** moderate 37, severe 96 (n=133)* **Group 2** **N:** No. randomised NR, 144 treated 1st attack, 133 treated 2nd attack as well **Age (mean):** 42±10(n=133)* **Gender F/M:** 111/22 (n=133)* **Drop outs:** NR **Usual severity of headache:** moderate 32, severe 101 (n=133)* * relates to patients who treated 2 attacks only	completely relieved. To maintain blinding patients in Sumatriptan group took a second dose of placebo DHE. Patients instructed to prepare both treatments (active & placebo) then to administer within 1 minute of each other. Rescue medication permitted if migraine symptoms not relieved after two hours. Ergotamine containing medications, DHE or Sumatriptan not permitted as rescue medications. Prophylactic medication excluding oral DHE permitted provided dosage remained unchanged during study.		* number calculated by NCGC	**Notes:** Outcome data relates to all patients who completed treatment for 2 attacks.
			Relief of clinical disability – reduction of functional ability from 2 (functional/working ability severely impaired) or 3 (bed rest required) to 0 (able to function normally) or 1 (functional/working ability impaired to some degree)	Actual numbers unclear. Reports 63% of patients in both groups were severely disabled or required bedrest pre-treatment. Reduction in disability significantly less in DHE group at all time points. **p values:** <0.001	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society, DHE=dihydroergotamine

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year Winner et al, 1996[857] **Study design:** RCT **Comparison:** Triptan vs dihydro-ergotamine **Setting:** In patient clinic **Duration of follow-up:** 24 hours	**Patient group:** Adults with migraine with or without aura. **Inclusion criteria:** Migraine with or without aura according to IHS criteria for at least 1 year; 1 to 6 moderate or severe attacks per month in the preceding 6 months; duration of migraine to be treated less than 12 hours, excluding aura; resolution of all previous migraine events within 72 hours with no permanent neurologic dysfunction; screening diastolic blood pressure of 90mmHg or less. Premenopausal women who were not surgically sterile or using an acceptable method of birth control were required to have negative results of a serum pregnancy test immediately before treatment. **Exclusion criteria:** History of chronic tension type or cluster headache, hemiplegic, aphasic or basilar migraine; duration of aura longer than 60 minutes; active psychiatric or neurologic disorders other than migraine; peripheral occlusive vascular disorders, including coronary artery disease; current use of macrolide antibiotics; significant hepatic or renal impairment; history of repeated treatment failures with	**Group 1 -** Sumatriptan (6mg) succinate injected subcutaneously into lateral aspect of thigh. **Group 2 -** Dihydroergotamine (DHE) (1mg) mesylate injected subcutaneously into lateral aspect of thigh. Patients receiving prophylactic treatment for migraine were permitted no change in the medication for at least 2 weeks before study dosing: <u>Prophylactics in Sumatriptan group</u> Calcium channel blockers: 9 Beta blockers: 16 Tricyclic derivatives: 21 <u>Prophylactics in DHE group</u> Calcium channel blockers: 14 Beta blockers: 18 Tricyclic derivatives: 28 Use of any form of ergot alkaloid or sumatriptan prohibited in 72 hours preceding drug administration. Use of	**Headache response at 2 hours** - reduction of headache severity from grade 2 (moderate) or 3 (severe) at baseline to 0 (none) or 1 (mild)	**Sumatriptan:** 128*/150 (85.3%) **DHE:** 106*/145 (73.1%) **p value:** <0.001	**Funding:** Sanchez Pharmaceuticals **Limitations:** Method of randomisation not reported and no mention of allocation concealment. Nurse administering treatment was not blinded to interventions. Unclear if investigator was blinded to patient characteristics, they were blinded to treatment. **Additional outcomes:** Pain relief at 3 & 4 hours; improvement in functional status at 3 & 4 hours; recurrence of headache at 24 hours; nausea; emesis; number of adverse events; physician's global evaluation of drug effectiveness. Proportion of patients pain free at 24 hours (unclear if efficacy population) **Notes:**
			2nd dose of treatment – patients without relief after 2 hours received a second dose of study drug.	**Sumatriptan:** 23/150 **DHE:** 43/145 **p value:** NR	
			Improvement in functional status at 2 hours – 3 categories: Able to function normally; "Struggle to carry on"; "Too ill to do anything".	**Sumatriptan:** 127*/150 (84.7%) **DHE:** 99*/145 (68.3%) **p value:** <0.001	
			Improvement in functional status at 4 hours – 3 categories: Able to function normally; "Struggle to carry on"; "Too ill to do anything".	**Sumatriptan:** 119*/150 (79.3%) **DHE:** 104*/145 (71.5%) **p value:** NS Unsure of denominators at 4 hours	
			Improvement in functional status at 24 hours – 3 categories: Able to function normally; "Struggle to carry on"; "Too ill to do	**Sumatriptan:** 121*/150 (80.7%) **DHE:** 128*/145 (88.3%) **p value:** NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	hypersensitivity to sumatriptan, ergotamine or dihydroergotamine in any dosage form; known physical or psychological dependence on addictive agents; chronic use (>3 days/week) of opioid or other analgesic; use of serotonin reuptake inhibitors. **All patients** **N:** 310 **Drop outs:** 15 **Group 1** **N:** 158 **Age (mean):** 41.5 (22-55) **Functional status:** Able to function normally - 0; "Struggle to carry on" – approx 2 thirds; "Too ill to do anything" – approx 1 third **Drop outs:** 8 **Group 2** **N:** 152 **Age (mean):** 40.5 (20 to 63) **Functional status**: Able to function normally - 3; "Struggle to carry on" – approx 2 thirds; "Too ill to do anything" – approx 1 third **Drop outs:** 7	antiemetics and narcotic analgesics was prohibited in 24 hours preceding drug administration. At 60 minute assessment intramuscular prochlorperazine edisylate (10mg) or, if contraindicated, metoclopramide hydrochloride (10mg) could be given for emesis. No other medications permitted. Patients discharged 2 hours after treatment if pain relieved. Those without relief 1 hour after 2nd dose could be given rescue medication of physician's choice but not ergotamines, dihydroergotamine, sumatriptan or steroids.	anything". **Serious adverse events**	Unsure of denominators at 24 hours **Sumatriptan:** 0/150 **DHE:** 0/145 **p value:** NS	* calculated by NCGC Patients attended pre-treatment screening then told to return to clinic when they next experienced a moderate or severe headache.

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