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Diclofenac-Potassium in Migraine
A Review

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Data Selection
Sources: Medical literature published in any language since 1966 on diclofenac-potassium, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.
Search strategy: AdisBase search terms were 'diclofenac-potassium' and 'migraine'. Medline and EMBASE search terms were 'diclofenac-potassium' and 'migraine'. Searches were last updated 17 April 1999.
Selection: Studies in patients with acute migraine who received diclofenac-potassium. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.
Index terms: diclofenac-potassium, migraine, pharmacokinetics, pharmacodynamics, therapeutic use.

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Summary

Abstract

The NSAID diclofenac is a potent inhibitor of prostaglandin synthesis and an established antipyretic and analgesic agent. Diclofenac-potassium was developed as an immediate-release tablet with the aim of providing rapid onset of action after oral administration. This formulation has been investigated in the acute treatment of migraine.

Data from available placebo-controlled clinical trials indicate that diclofenac-potassium 50 or 100mg as an immediate-release tablet is more effective than placebo and as effective as oral sumatriptan 100mg and ergotamine plus caffeine at reducing pain intensity in patients with migraine 2 hours after initial administration. Duration of pain relief is similar for the 3 drugs but onset appears to be faster with diclofenac-potassium than with oral sumatriptan or ergotamine plus caffeine.

Diclofenac-potassium appears to have favourable effects on some accompanying symptoms such as nausea and vomiting. The frequency of these symptoms was significantly lower with diclofenac-potassium than with sumatriptan in 1 study, although only a few patients had vomiting at baseline. Effects on phonophobia or photophobia did not differ between diclofenac-potassium, sumatriptan and ergotamine plus caffeine.

The need for rescue medication is consistently less with diclofenac-potassium than with placebo. Data are inconsistent or scarce regarding the effects of diclofenac-potassium versus placebo on other measures such as headache recurrence and working ability.

Diclofenac-potassium was generally well tolerated in clinical trials in patients with migraine. Adverse events reported most frequently (abdominal pain, tiredness and fatigue and nausea) were typically mild to moderate.

Conclusion: Diclofenac-potassium provides rapid pain relief (within 60 to 90 minutes), is well tolerated and reduces the frequency of some of the accompanying symptoms in patients with migraine. Available trials indicate that diclofenac-potassium provides similar pain relief to sumatriptan and is at least as effective as ergotamine plus caffeine, but appears to have a greater effect on nausea and vomiting than sumatriptan and a faster onset of action than both drugs. Comparisons with other NSAIDs are lacking. Diclofenac-potassium is likely to find a role as a useful first-line option in the acute treatment of migraine.

1. Rationale for the Use of Diclofenac-Potassium in Migraine

There are 2 different strategies for the management of migraine:

- preventative therapy (i.e. prophylaxis) to reduce the frequency, severity and duration of attacks in patients who experience more than 3 migraine episodes per month
- abortive therapy (i.e. management of migraine attacks) to reduce the severity and duration of headache pain and the associated symptoms once an attack has started.[1]

Prior to any treatment, it is important that correct diagnosis of the condition is established;[2] numerous guidelines are available for the diagnosis of headache and migraine.[2-5] Migraine has been described by the Headache Classification Committee of the International Headache Society (IHS) as a recurring, moderate to severe headache which is usually unilateral and pulsating; each attack may last from 4 to 72 hours and may be associated with an aura.[6] The aura is a complex of focal neurological symptoms which may precede or accompany the migraine attack. Migraine may be aggravated

by routine physical activity and is commonly associated with nausea, vomiting, photophobia and phonophobia.[6]

Although the exact mechanism of migraine is unclear,[7] there are several hypotheses regarding its pathogenesis. The 'vascular theory' suggests that vasoconstriction and/or vasodilation of cerebral vessels account for, respectively, the aura and throbbing phases of a migraine headache. A variety of vasoactive substances including 5-hydroxytriptamine (serotonin) and prostaglandins are thought to be involved, although their exact roles are not clear. Serotonin, for example, can produce vasoconstriction or vasodilation *in vitro* depending on the preexisting vascular tone, the vascular tissue type and the concentration applied. The 'neural theory' suggests that a dysfunction of nerve cells and neurotransmitters such as serotonin may be responsible.[7] These theories are discussed in more detail elsewhere.[8,9]

Irrespective of the mechanism, the outcome of most migraine attacks is head pain, the symptom from which most patients with migraine seek relief.[3] Migraine headache has been reported to take between 0.5 and 3 hours to reach maximum intensity.[7] Therefore, antimigraine agents should provide a rapid onset of pain relief.

The nonsteroidal anti-inflammatory (NSAID) diclofenac is a potent inhibitor of prostaglandin synthesis and an established antipyretic and analgesic agent.[10] Available proprietary oral preparations of diclofenac differ in the type of salt used (sodium or potassium) and in the tablet formulation (enteric-coated or immediate-release) which influences the release characteristics of the drug. Diclofenac-sodium is formulated as an enteric-coated or extended-release tablet to give a prolonged slow release of the active drug after administration and is indicated in chronic pain conditions such as osteo- and rheumatoid arthritis.[11] Diclofenac-potassium, which has a higher solubility in water than the sodium salt,[12] was developed as an immediate-release tablet to provide rapid onset of action after oral administration. This formulation is indicated in acute pain conditions such as primary dysmenorrhoea and dental pain.[11]

The rationale for the investigation of oral diclofenac-potassium in the management of migraine is the proven analgesic properties of diclofenac in other acute pain conditions.

2. Pharmacology

Specific pharmacodynamic and pharmacokinetic studies of diclofenac-potassium have not been performed in patients with migraine.[12] There are, however, several published reports investigating diclofenac-potassium in non-migraine acute pain conditions which are discussed in section 2.1.1. Studies performed using the sodium salt and/or studies in other patient populations and volunteers are used in this article to demonstrate the pharmacology of the drug. Where necessary, unpublished data are used to supplement this information.

2.1 Pharmacodynamic Properties

The pharmacodynamic properties of diclofenac-sodium (including analgesic, anti-inflammatory and antipyretic effects) are comprehensively reviewed elsewhere.[10] The therapeutic efficacy of diclofenac in migraine (section 3) is largely attributable to the drug's analgesic properties;[13] its anti-inflammatory effects may also play a role. Both of these effects are thought to result from inhibition of prostaglandin synthesis;[13] however, the precise mechanism of action has not been determined.

2.1.1 In Non-Migraine Acute Pain Conditions

Studies discussed in this section demonstrate that diclofenac-potassium is an effective analgesic with a rapid onset of action in patients with various acute pain states. Generally, trials were randomised, double-blind, double-dummy, parallel-group and placebo-controlled; patient numbers ranged from 60 to 225 per treatment group.

Where stated, pain intensity and pain relief were measured using 4-point verbal scales in patients,[14,15] or nociception threshold levels above baseline in volunteers.[16]

Results from the studies discussed in this section should be viewed with caution, however, since it is not certain whether these data can be extrapolated to the clinical setting of migraine (section 3).

Analgesia

Single-dose diclofenac-potassium 50mg or 100mg was superior to aspirin 650mg in reducing pain in patients after tooth extraction[17] or episiotomy ($p \leq 0.05$).[15] Also, in patients with ankle sprain, diclofenac-potassium 50mg 3 times daily for 7 days was superior to ibuprofen 400mg 3 times daily[18] or piroxicam 20mg once daily[19] in reducing pain on walking ($p < 0.05$ days 1 to 3),[18,19] pain on palpation ($p < 0.01$ *vs* ibuprofen at day 3)[18] or pain at rest ($p < 0.0002$ *vs* piroxicam and $p < 0.05$ *vs* ibuprofen at day 2).[18,19]

Onset of Effects

The onset of action is more rapid with diclofenac-potassium than with aspirin or ibuprofen and faster than or equal to that of piroxicam. As assessed by mean pain intensity difference scores, the analgesic effect of diclofenac-potassium 50mg (n = 50) or 100mg (n = 51) was significantly greater than that of aspirin 650mg (n = 50) as early as 0.5 hours after a single-dose administration in patients with acute episiotomy pain ($p \leq 0.05$).[15]

In patients with mild to severe ankle sprain, pain relief on walking[18] or at rest[19,20] was apparent 1 hour after administration of diclofenac-potassium 50mg. At this time, analgesia for pain relief on walking was better with diclofenac-potassium than with ibuprofen 400mg ($p < 0.03$),[18] and better than ($p = 0.0004$)[19] or similar to[20] that achieved with piroxicam 20mg.

The difference in the galenic preparations of the 2 diclofenac salts may have an effect on the dissolution and absorption time (section 2.2.1) and subsequently the onset of effect. A placebo-controlled comparative study (n = 151) using the dental pain model (i.e. pain after tooth extraction)[14] demonstrated a more rapid onset of analgesia with the immediate-release potassium formulation than with the enteric-coated sodium salt of diclofenac (fig. 1).

Mean pain intensity was significantly reduced within 0.25 hours with the potassium salt and within 2 hours with the sodium salt (both $p < 0.05$ *vs* placebo).[14] Lowest mean pain intensity scores occurred at 2 hours with the potassium salt and about 3 hours with the sodium salt.

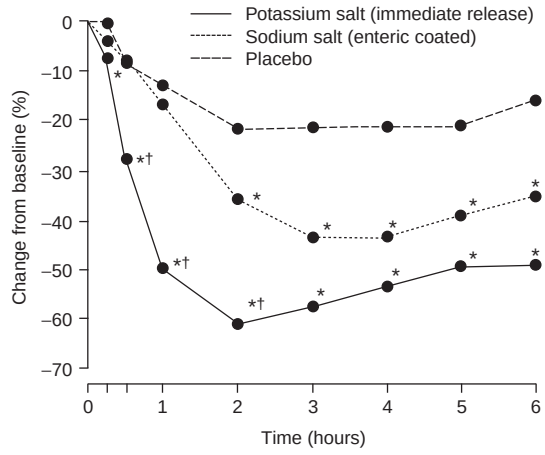

Fig. 1. Onset of effects for diclofenac-potassium versus diclofenac-sodium. Onset of effect assessed by change in baseline pain intensity scores after single-dose oral administration of diclofenac-potassium 50mg (n = 51), diclofenac-sodium 50mg (n = 54) or placebo (n = 46) in patients after tooth extraction (a pain model).[14] * $p < 0.05$ *vs* placebo; † $p < 0.05$ *vs* diclofenac-sodium.

2.2 Pharmacokinetic Properties

The pharmacokinetics of the sodium salt of diclofenac have also been comprehensively reviewed elsewhere.[10] In this review, only the absorption kinetics of orally administered diclofenac-potassium are specifically discussed.

The potassium salt is formulated to dissolve in the acid conditions of the stomach, whereas the delayed release preparations of the sodium salt are intended to dissolve later in the more alkaline conditions of the duodenum.[15] Once dissolved (and thus dissociated from the salt), the active diclofenac moiety in each preparation is distributed, metabolised and eliminated in the same manner.[12] Table I summarises the pharmacokinetic properties of diclofenac after absorption.

2.2.1 Absorption of Oral Diclofenac-Potassium

Peak plasma concentrations (C_{max}) of diclofenac occur about 1 hour (range 0.33 to 2 hours)

after oral administration of the potassium salt in fasted volunteers.[11,13] Rapid absorption from the gastrointestinal tract is suggested by the detection of diclofenac in plasma within 10 minutes of taking oral diclofenac-potassium in some fasted individuals.[13]

The presence of food decreases the rate of diclofenac absorption after oral administration of the potassium salt, as indicated by a reduction in C_{max} and an increase in time to C_{max} (t_{max}) in volunteers (both by approximately 30%).[11,13]

Unpublished data from a total of 634 individuals show that, although the C_{max} and overall bioavailability of the 2 diclofenac salts at the same plasma concentration are similar, the immediate-release potassium salt has a 3-fold shorter t_{max} than the enteric-coated sodium salt and an approximate 20 times faster onset of absorption (defined as the last time point with plasma concentration below the limit of assay detection) [fig. 2].[12]

These data are consistent with a more rapid onset of activity with the immediate-release potassium salt compared with the enteric-coated sodium salt formulation of diclofenac (section 2.1.1).

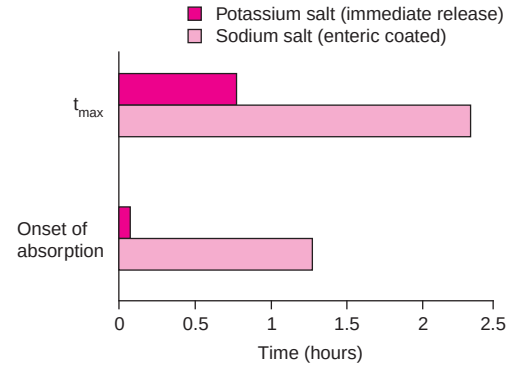

Fig. 2. Speed of absorption with diclofenac-potassium versus diclofenac-sodium. Time to maximum plasma concentration (t_{max}) and onset of absorption (defined as the last time point with plasma concentration below the limit of assay detection) after oral administration in 473 diclofenac-potassium and 161 diclofenac-sodium recipients (type of individual not defined; no statistical analysis provided).[12]

3. Therapeutic Efficacy

There are several published studies[21-23] pertaining to the use of diclofenac-potassium in migraine, including a comparison with oral sumatriptan.[23] These studies are randomised, placebo-controlled, double-blind and within-patient in design. One trial, a comparison with ergotamine plus caffeine, has been published as an abstract.[22] Results from these studies are supported by unpublished data from a parallel-group trial in 423 patients that compared diclofenac-potassium and ergotamine plus caffeine.[24]

Where reported, patients fulfilled the IHS diagnostic criteria for migraine[21] or had average visual analogue scale (VAS; 0 = no pain to 100mm = excruciating pain requiring bed rest) scores of approximately 50mm[23,24] at baseline. The duration of migraine ranged from 1 to 54 years[21,23] and the frequency of attacks ranged between 1 and 12 per month[21,24,25] (medians, where reported, were 3[24] and 3.8[21] per month). Patients experienced migraines with or without aura.[21,23,24]

In 1 study,[23] the use of β-blockers or calcium antagonists was allowed at a constant dosing regimen throughout the trial; in another,[21] prophylactic medication was halted ≥2 weeks prior to the start of the study.

Where stated, medication was taken at the earliest sign of a migraine headache and a period of

Table I. Pharmacokinetic properties of oral diclofenac after absorption[10]

Distribution
Like other nonsteroidal anti-inflammatory drugs (NSAIDs) diclofenac is highly protein bound (≥99.5%)
Diclofenac crosses the placenta and has been found in small amounts in breast milk
Metabolism
Undergoes significant first-pass metabolism; only 60% of the active drug reaches the systemic circulation unchanged after oral administration
Elimination
Initially by hepatic metabolism and subsequently by urinary and biliary excretion
Age and renal or hepatic impairment do not appear to significantly influence the plasma concentrations of unchanged diclofenac

≥48 hours was required between treated attacks.[21,23] A washout period of at least 3 days between the last migraine treatment and the start of study was required in 1 trial,[21] whereas another trial required 2 days.[24]

The efficacy end-points used in the studies reviewed were in accordance with those recommended by the IHS guidelines for clinical trials in migraine.[26] The common primary end-point in all studies was headache pain intensity at 1[22] or, more commonly, 2[21,23,24] hours after initial administration of test medication. This was assessed using 100mm VAS (defined above,[23] 0 = no pain to 100mm = unbearable pain[21]), or a 4-point verbal scale (grade 1 = none to grade 4 = severe).[21]

Stratification according to baseline headache severity was not performed in these studies, nor were patients with severe headaches excluded from treatment.

Secondary end-points included VAS measured at other time points, the presence of accompanying symptoms (i.e. nausea, vomiting, phonophobia and photophobia),[21-24] working ability (assessed using a 4-point scale; lowest point = normal, highest point = much impaired[21] or required bed rest[23]) and the need for rescue medication (permitted 2 hours after initial test medication).[21,23,24] One study provided information on headache recurrence (defined as symptom recurrence within 48 hours after resolution of initial attack).[23]

3.1 Effects on Pain Intensity

Diclofenac-potassium 50 or 100mg significantly reduced migraine pain intensity within 1 to 2 hours after initial administration, compared with placebo (table II). There were no significant differences between the 2 doses of diclofenac-potassium.[21,23]

Two hours after the initial test medication, headache improved from grade 4/3 to grade 2/1 in significantly more diclofenac-potassium 50 or 100mg recipients than in those receiving placebo (39, 44 and 22%, respectively; $p < 0.05$ for active drug *vs* placebo).[21] In 1 study, 1 dose of 50mg of diclofenac-potassium was found to be effective in relieving migraine headache compared with placebo at 2 hours after initial test medication, as assessed using the VAS ($p = 0.007$).[24]

There were no significant differences in measures of pain relief between diclofenac-potassium 50 or 100mg or sumatriptan 100mg[23] between diclofenac-potassium and ergotamine plus caffeine, or between ergotamine plus caffeine and placebo at 2 hours[24] (table II). However, diclofenac-potassium reduced pain more effectively than ergotamine plus caffeine at 1 hour in 1 trial;[22] in another,[24] pain intensity at 1 hour after treatment was also significantly different, compared with placebo, with diclofenac-potassium 50mg but not with ergotamine plus caffeine.

Overall pain relief (assessed as the mean area under the curve of the mean VAS scores from 0 to 8 hours after administration) was significantly greater with both dosages of diclofenac-potassium, sumatriptan, or ergotamine plus caffeine than with placebo ($p < 0.001$).[23,24]

Time to significant reduction in pain relief was faster with diclofenac-potassium 50 or 100mg than with sumatriptan 100mg.[23] Compared with placebo, reductions in pain intensity [measured as reduction (mm) from placebo VAS score] were significant from 1 hour after diclofenac-potassium [–7.08mm; 95% confidence intervals (CI) –12.05 to –2.11mm for 50mg and –7.79mm; CI –12.81 to –2.77mm for 100mg] and from 1.5 hours (–8.29mm; 95% CI = –14.04 to –2.53mm) after sumatriptan administration. Pain intensity remained significantly below that with placebo throughout the entire 8-hour observation period with each test medication;[23] observations after 8 hours were not performed in this study.

The duration of the migraine attack was reduced with either diclofenac-potassium 50 and 100mg or sumatriptan 100mg compared with placebo [mean (median) duration of about 27 (11) hours for each active treatment and 47 (72) hours for placebo].[23] The duration of attack was significantly longer in patients treated with diclofenac-potassium 50mg than in those given ergotamine plus caffeine (mean 15 *vs* 11 hours, no p value given), but no difference was seen between either active treatment and

Table II. Efficacy of oral diclofenac-potassium (DIC) versus placebo or other active treatments in patients with migraine

Reference	Study design (no. of evaluable patients)	Drug	Regimen	Change in pain intensity[a]			Patients requiring rescue medication[b] (%)	Overall efficacy
				versus baseline (%)	versus SUM or ERG+CAF (mm)	versus PLA (mm)		
Diclofenac-K/Cafergot Migraine Study Group[24]	db, r, dd, pg (140)	DIC 50mg	Single dose of 1 tablet plus additional tablets as needed after 2 hours (maximum 4 tablets per attack)	–20[c]	–3.6	–9.0**		DIC > PLA
	(144)	ERG 1mg +CAF 100mg	Single dose of 2 tablets plus additional tablets as needed after 2 hours (maximum 5 tablets per attack)	–12[c]		–5.4		DIC ≡ ERG+CAF
	(146)	PLA		+5[c]				
Cortelli et al.[12,22]	db, r, wp (63)	DIC 50mg	Single dose of 1 tablet plus additional tablets if needed (up to 3 tablets per attack)		–11.9[†]	–14.7**		DIC > PLA
		ERG 1mg + CAF 100mg	Single dose of 2 tablets plus additional tablets if needed (up to 6 tablets per attack)			–2.8		DIC > ERG+CAF
		PLA						
Dahlöf & Björkman[12,21]	db, dd, mc, r, wp (64)	DIC 50mg	Single dose of test medication used for each of 3 consecutive attacks	–30[c]		–14.6***	46	DIC 50mg ≡ DIC 100mg > PLA
		DIC 100mg		–39[c]		–11.7**	37*	
		PLA		–13[c]			58	
Diclofenac-K/ Sumatriptan Migraine Study Group[23]	db, dd, mc, r, wp (115)	DIC 50mg	Single dose of test medication used for each of 4 consecutive attacks over a period of 3 months	–48	–2.5	–17***	36*[d]	DIC 50mg ≡ DIC 100mg ≡ SUM > PLA
		DIC 100mg		–56	–4.1	–18.6***		
		SUM 100mg		–42		–14.5***	41*	
		PLA		–16			60	

a Assessed at primary end-point (1[22] or 2 hours[21,23,24]) after initial drug administration using VAS (0 to 100mm; 0 = no pain to 100mm = unbearable pain[21] or excruciating pain requiring bed rest).[23] Data versus baseline are expressed as percentage reduction from baseline VAS score at primary end-point. Data versus PLA and comparators are expressed as estimated least squares mean difference in the VAS at primary end-point.

b Rescue medications permitted 2 hours after initial test medications.

c Estimated from graph.

d Data for diclofenac-potassium 50mg or 100mg.

CAF = caffeine; **co** = crossover; **db** = double- blind; **dd** = double-dummy; **ERG** = ergotamine; **mc** = multicentre; **NS** = not statistically significant different; **pg** = parallel group; **PLA** = placebo; **r** = randomised; **VAS** = visual analogue scales; **wp** = within patient; ≡ indicates not significantly different from; **>** indicates more effective than, p < 0.05; * p < 0.05, ** p < 0.01, *** p < 0.001 *vs* PLA; † p < 0.05 *vs* ERG+CAF.

placebo (12 hours). Whether the use of repeat or rescue medication may have affected these results is unknown.[24] Patients who needed rescue medication before the end of the attack were assigned a set duration of 72 hours, which is the usual maximum duration of an untreated migraine attack, before taking the medication.[23,24]

3.2 Effects on Accompanying Symptoms

3.2.1 Nausea and Vomiting

Diclofenac-potassium 50 or 100mg tended to reduce the incidence of nausea more than placebo in 1 study[21] and at various time points was superior to placebo and the comparators sumatriptan[23] and ergotamine plus caffeine[24] in larger trials.

In 1 large trial,[23] about 43 to 53% of patients had nausea at baseline. After 2 hours, both doses of diclofenac-potassium were superior to placebo and sumatriptan at reducing nausea (fig. 3). After 8 hours, all active treatments were better than placebo at reducing this symptom (all $p < 0.05$), but only diclofenac-potassium 50mg was significantly better than sumatriptan ($p < 0.05$). In the other large trial,[24] diclofenac-potassium 50mg was superior to ergotamine plus caffeine in reducing nausea at 1, 2 and 4 (but not 6) hours after a dose and was superior to placebo at 1 and 4 hours after a dose.

The incidence of vomiting was significantly reduced with both dosages of diclofenac-potassium compared with sumatriptan at 2 (fig. 3) and 8 hours after initial administration and with the 50mg dose compared with placebo at 8 hours.[23] Vomiting was also significantly reduced ($p < 0.05$) with diclofenac-potassium 50mg, but not ergotamine plus caffeine, versus placebo throughout a 6-hour observation period in the larger study.[24]

It should be noted that in trials assessing this parameter vomiting was infrequent (about 5 to 10% of the total study population)[21,23,24] and these results should be interpreted with caution.

3.2.2 Photophobia and Phonophobia

The effect of diclofenac-potassium on photophobia 2 hours after administration is unclear. In 1 study ($n = 58$),[21] the odds ratio for absence of symptoms with diclofenac-potassium 100mg was 1.23 (95% CI 0.76 to 1.99) relative to diclofenac-potassium 50mg and 1.82 (95% CI 1.07 to 3.09) relative to placebo.

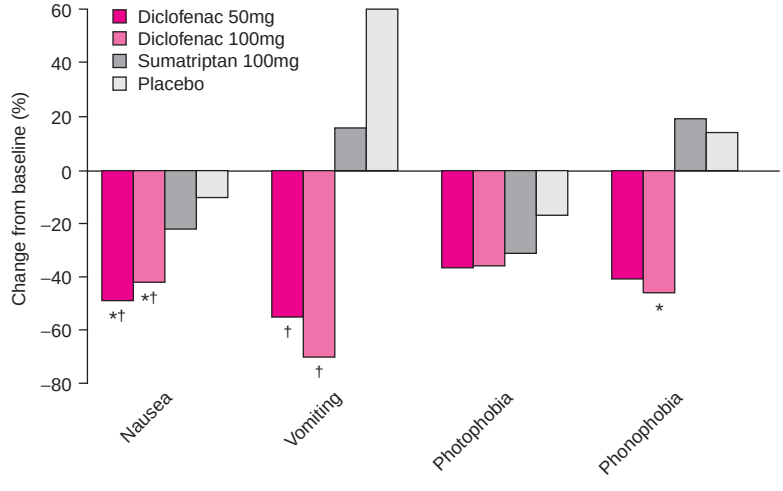

Fig. 3. Effect of diclofenac-potassium 50mg and 100mg, sumatriptan 100mg or placebo on the accompanying symptoms of migraine headache.[23] Assessments were made 2 hours after oral administration of test medication in each of 4 successive migraine attacks in 115 patients participating in a randomised double-blind crossover study. * $p < 0.05$ *vs* placebo; † $p < 0.05$ *vs* sumatriptan.

In a larger study,[23] there was no significant difference between diclofenac-potassium 50 or 100mg, sumatriptan 100mg and placebo after 2 hours, despite a tendency towards greater reduction with the active treatments (fig. 3).[23] Eight hours after administration, however, both dosages of diclofenac-potassium reduced the incidence of photophobia by about 60% compared with placebo ($p < 0.05$).[23]

Similarly, diclofenac-potassium 100mg significantly reduced the incidence of phonophobia at 2 hours, compared with placebo.[21,23] Diclofenac-potassium 50mg versus diclofenac-potassium 100mg did not show a significant difference in decreasing phonophobia.[21] The incidence of photophobia and phonophobia did not differ among patients treated with diclofenac-potassium 50mg, ergotamine plus caffeine, or placebo.[24]

3.3 Working Ability

Working ability assessed 2 hours after initial administration of test medication was improved to a significantly greater extent with diclofenac-potassium 50mg[24] (no p value provided in manuscript) or 100mg[21] than with placebo ($p = 0.001$) in 1 study,[21] but in another larger study,[23] there was no statistically significant difference between diclofenac-potassium 50mg, 100mg, sumatriptan 100mg or placebo.

3.4 Use of Rescue Medication

Use of rescue medication (permitted 2 hours after initial test medication) was less common in patients taking diclofenac-potassium 50mg or 100mg than placebo.[21,23] Rescue medication was required by 36 to 46% of patients receiving diclofenac-potassium 50mg or 100mg and by approximately 60% of placebo recipients in 2 separate studies.[21,23] This difference was significant for diclofenac-potassium 100mg versus placebo (odds ratio 1.82; 95% CI 1.15 to 2.89) in 1 study.[21] In a second study, 41% of sumatriptan recipients (versus 36% of diclofenac-potassium 50 or 100mg recipients) also required rescue medication.[23] In this latter study, differences between all active treatments (diclofenac-potassium 50 and 100mg and sumatriptan) and placebo were significant.[23]

Mean time to first intake of rescue medication was 13, 11, 13 and 8 hours, respectively, for diclofenac-potassium 50mg, 100mg, sumatriptan 100mg and placebo.[23] In another study, this parameter did not differ significantly among patients given placebo, diclofenac-potassium 50mg or ergotamine plus caffeine.[24]

3.5 Other End-Points

Headache recurrence within 48 hours of resolution of initial attack, although more frequent with diclofenac-potassium (22 and 24%) and sumatriptan (26%) than with placebo recipients (19%), did not differ significantly among groups. In patients not taking rescue medications, headache recurred in 8, 12, 6 and 4% of diclofenac-potassium 50mg, 100mg, sumatriptan 100mg and placebo recipients, respectively. Corresponding recurrences in patients who did take rescue medication were 14, 11, 20 and 15% (not significantly different).[23]

In 1 study,[21] 52, 25 and 23% of 44 patients selected diclofenac-potassium 100mg, 50mg or placebo as their respective first choice preference for treatment (no statistical analysis provided). There was no significant difference in patients' overall evaluation of diclofenac-potassium 50mg, 100mg or sumatriptan 100mg treatment in the other comparative trial. Approximately 50% of patients receiving active treatments and 20% of those receiving placebo rated overall efficacy as 'good' or 'excellent'. It was stated in this trial that diclofenac-potassium 50 and 100mg and sumatriptan were significantly superior to placebo.[23]

4. Tolerability

4.1 General Profile

Diclofenac-potassium was generally well tolerated in clinical trials in patients with migraine.[21-24] In a placebo-comparative study,[21] approximately 90% of all patients felt that the test medication was well tolerated. Tolerability was evaluated as 'good' or 'excellent' by approximately 70% of patients

receiving diclofenac-potassium 50mg, 100mg, sumatriptan 100mg or placebo.[23] The severity of adverse events reported was typically mild to moderate;[21,23] severe adverse events were reported in 0[23] or 1%[21] of patients.

Adverse events reported most frequently in separate clinical trials included abdominal pain,[23,24] tiredness and fatigue[21,23,24] and nausea.[21,24] Investigators reported some difficulty in differentiating between drug- and migraine-induced symptoms.

Patients reported fewer adverse events when taking diclofenac-potassium than when taking sumatriptan: 15, 12, 31 and 18% of patients taking diclofenac-potassium 50mg, 100mg, sumatriptan 100mg and placebo, respectively, reported adverse events (rated by the investigator as possibly, probably or highly probably related to the trial drug; no p values provided). Adverse events with a ≥5% incidence were somnolence and abdominal pain in diclofenac-potassium recipients and abdominal pain, fatigue, dizziness, and tachycardia with sumatriptan.[23]

4.2 Hepatic Events

There has been some concern over the large number of reports of hepatitis and jaundice associated with the use of diclofenac-sodium for chronic pain management in the US (over 180 cases reported to the FDA; no further details).[27] In addition, several case reports indicate that hepatitis has resulted from use of diclofenac (salt not defined; presumed sodium) in Australasian patients with chronic pain.[28] In most of the patients in this latter study,[28] hepatic adverse events were not apparent until at least 6 weeks after initiation of diclofenac 75mg daily.

Similar hepatic events would not be expected with diclofenac-potassium in the management of migraine, since the drug should be used intermittently and for short periods only. Nevertheless, the product information carries a warning regarding the use of diclofenac-potassium in patients with hepatic porphyria (section 5.1).

5. Dosage and Administration

The recommended dosage of diclofenac-potassium for the treatment of migraine is 50mg initially at the first sign of an impending attack. Another 50mg dose may be taken if pain is not relieved within 2 hours of the first dose. Further doses of 50mg may be taken at intervals of 4 to 6 hours, if needed, to a maximum of 200mg per attack.[29]

5.1 Contraindications and Warnings

Diclofenac-potassium (as with all other forms of diclofenac) should not be given to patients with hepatic porphyria or a history of asthma, urticaria or other allergic-type reactions after administration of aspirin or other NSAIDs.[11]

Oedema and fluid retention have been observed in some patients taking diclofenac; therefore, diclofenac-potassium should be used with caution in patients with cardiac decompensation, hypertension or other conditions predisposing to fluid retention.[11]

Peptic ulceration and gastrointestinal bleeding have been reported in patients taking diclofenac-sodium. In patients with adrenal insufficiency, prolonged corticosteroid therapy should be tapered rather than abruptly discontinued when diclofenac is added to the treatment.[11] These situations may not be a problem with the potassium salt since it is not expected to be taken continuously over long periods of time for the management of migraine.[11]

5.2 Drug Interactions

Concomitant administration of diclofenac and aspirin is not recommended, as aspirin displaces diclofenac from binding sites, resulting in lower plasma diclofenac concentrations.[11] Although interaction between diclofenac and warfarin-like anticoagulants has not been shown, caution is advised with concomitant administration of these agents. In addition, the toxicity of digitoxin, methotrexate, cyclosporin and lithium may be increased with concomitant administration of diclofenac.[11]

6. Place of Diclofenac-Potassium in the Management of Migraine

The epidemiology and socioeconomical impact of migraine have been extensively documented.[30-35] Briefly, migraine primarily affects individuals from young adulthood up to their late 50s. This is, potentially, their most productive working period. Population-based studies in several countries including France, Canada and the US concur that the prevalence of migraine is up to 3 times greater in females than in males (reviewed by Lipton et al.[30]).

A large proportion of patients with migraine are self-diagnosed (i.e. they have never consulted a physician) and/or rely on self-medication with over-the-counter (OTC) products.[30,36] For example, in the US, only 40% of women and 28% of men were reported to use prescription medicines to manage their migraine (reviewed by Gilkey and Ramadan[36]). This situation is not entirely satisfactory since diagnosis may be incorrect and the medication selected may not be appropriate for the individual.

Recent interest in diclofenac-potassium has focused on its efficacy as an abortive therapy for migraine. Data are available from 4 clinical trials but in some instances these are incompletely reported or unpublished.

Rapid onset of pain relief is essential in treating migraine attacks. Immediate-release diclofenac-potassium tablets were designed for rapid dissolution and absorption via the stomach. This is shown by the rapid onset of absorption of this formulation (10 minutes in a dental pain model; no similar data are available for patients with migraine). Pain relief with diclofenac-potassium, compared with placebo, is significant within 60 to 90 minutes in patients with migraine and persists for up to 8 hours.

For mild migraine attacks, simple analgesics such as aspirin, paracetamol (acetaminophen) and other NSAIDs (e.g. ibuprofen, naproxen, mefenamic acid and indomethacin) are given orally as the first line of drug treatment.[2] They should be started as early as possible in the attack. Often these agents are given in combination with an antiemetic such as metoclopramide to aid absorption and combat nausea.[4] On the basis of available information in patients with migraine, use of a concomitant antiemetic does not appear to be necessary with diclofenac-potassium, although no studies have assessed such combinations.

Diclofenac-potassium reduced the accompanying symptoms of migraine in some clinical trials. Nausea and phonophobia, for example, were significantly reduced from baseline 2 hours after test medication with diclofenac-potassium compared with placebo in 1 study; the effects of the drug on photophobia at 2 hours were unclear, but at 8 hours diclofenac-potassium significantly reduced this symptom compared with placebo (section 3.2.2). The drug also appears to reduce the frequency of vomiting, although in the studies reviewed, the small number of patients with vomiting at baseline precludes any firm conclusions.

The potential for NSAIDs to cause adverse gastrointestinal events is well known. Common symptoms include dyspepsia, heartburn, nausea, vomiting constipation/diarrhoea and, rarely, gastric bleeding.[8] Most of these drug-related adverse events occurred infrequently, if at all, in the short term clinical trials of diclofenac-potassium in patients with migraine, although tolerability data are limited. Indeed, as previously mentioned, nausea was reduced and gastric bleeding was not reported in any of the trials reviewed. The lack of gastrointestinal events is likely related to the short, intermittent duration of diclofenac-potassium therapy in migraine, unlike long term therapy with diclofenac-sodium or other NSAIDs which is required for chronic conditions such as arthritis.

Diclofenac-potassium may therefore have theoretical advantages over other NSAIDs for mild migraine attacks when several factors are considered together. The drug has a relatively rapid onset of action, an acceptable tolerability profile and may not require concomitant antiemetic compounds to combat nausea and enhance gastric absorption. However, comparative studies of orally administered diclofenac-potassium and other oral NSAIDs in migraine are currently unavailable and are re-

quired before these putative advantages can be confirmed.

In the presence of severe gastrointestinal symptoms (e.g. vomiting and nausea) a non-oral route of administration may be preferred (e.g. suppositories, nasal sprays and subcutaneous or intramuscular injections). Diclofenac-potassium is not available as a parenteral preparation. However, intramuscular diclofenac-sodium produced complete resolution of headache pain within 30 minutes in up to 88% of recipients.[37,38] If these results are confirmed, this preparation may be an alternative option when diclofenac is desired for rapid pain relief in migraine.

For moderately severe migraine attacks, effective drugs include high dose NSAIDs, nonselective serotonin antagonists (e.g. dihydroergotamine and ergotamine) and selective serotonin receptor antagonists such as sumatriptan.[39] The available comparative clinical trials appear to show that diclofenac-potassium has similar overall efficacy to sumatriptan and is at least as effective as ergotamine plus caffeine.

In 1 study, oral diclofenac-potassium 50mg or 100mg was as effective as oral sumatriptan 100mg in patients with migraine at relieving pain and had a slightly faster onset time (by 30 minutes). It was also significantly better than sumatriptan at reducing nausea and vomiting. There were no statistically significant differences between diclofenac-potassium and sumatriptan treatment phases for the effects on headache recurrence. The use of rescue medications is consistently less with diclofenac-potassium than with placebo and similar to that with sumatriptan.

Another important aspect which may influence treatment choice is cost. The economic burden of migraine to society may be divided into direct costs, including the primary cost of medical care, and indirect costs, including absence from work/education centre, decreased productivity at work and the economic consequences of disruption in other roles (e.g. the need for child care when a parent is unwell).[31] The indirect costs for migraine outweigh the direct costs.[30,31]

Sumatriptan is recommended as an initial single 25 to 100mg dose.[40] In some clinical trials, an initial single 50mg dose of diclofenac-potassium was effective. The acquisition costs of sumatriptan are higher than those of diclofenac-potassium[11,40] but, based on limited data, both drugs appear to have similar effects on working ability, which affects indirect costs. Formal cost-effectiveness studies are therefore needed to address all cost-related issues before the comparative pharmacoeconomics of the 2 agents are known.

In conclusion, diclofenac-potassium provides rapid pain relief (within 60 to 90 minutes), is well tolerated and reduces the frequency of some of the accompanying symptoms in patients with migraine. Available trials indicate that diclofenac-potassium provides similar pain relief to oral sumatriptan and is at least as effective as ergotamine plus caffeine, but appears to have a greater effect on nausea and vomiting than sumatriptan and a faster onset of action than both drugs. Comparisons with other NSAIDs are lacking. Diclofenac-potassium is likely to find a role as a useful first-line option in the management of migraine.

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