Migraine: pharmacotherapy in the emergency department

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Abstract
Migraine can be a disabling condition for the sufferer. For the small number of patients who fail home therapy and seek treatment in an emergency department, there are a number of therapeutic options. This paper reviews the evidence regarding the effectiveness and safety of the following therapies: the phenothiazines, lignocaine, ketorolac, the ergot alkaloids, metoclopramide, the "triptans", haloperidol, pethidine and magnesium. Based on available evidence, the most effective agents seem to be prochlorperazine, chlorpromazine and sumatriptan, each of which have achieved greater then 70% efficacy in a number of studies.

Keywords: migraine

Migraine headache can be a disabling condition for the sufferer. The patient and their general practitioner successfully manage most migraine headaches. However, a small number fail to respond and sufferers may present for treatment at emergency departments (ED). As most patients have tried oral medications before attending the ED, other routes of administration (usually parenteral) are most often used in ED. This review will focus on the agents that may be used to treat migraine in ED and the evidence supporting their use.

Definitions
Most of the research in the area of migraine focuses on so called common migraine or migraine without aura. The Headache Classification Committee of the International Headache Society defines migraine without aura as an "idiopathic, recurring headache disorder manifesting in attacks lasting 4–72 hours. Typical characteristics are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea, photophobia and phonophobia." The rarer migraine with aura is described as an "idiopathic, recurring headache disorder manifesting with attacks of neurological symptoms unequivocally localisable to the cerebral cortex or brain stem, usually developing gradually over 5–20 minutes and lasting less than 60 minutes. Headache, nausea and/or photophobia usually follow neurological aura symptoms directly or after a free interval of less than an hour. The headache usually lasts less than 72 hours, but may be completely absent." At least two typical episodes are needed before this diagnosis can be assigned. In addition, there are a number of uncommon variants such as ophthalmoplegic and abdominal migraine.

Pathophysiology
The pathophysiology of migraine is complex and our understanding continues to evolve. Events implicated in migraine initiation include altered electrical activity ("cortical spreading depression"), a failure of brain ion homeostasis, an efflux of excitatory amino acids from nerve cells and increased energy metabolism. N-methyl-D-aspartate (NMDA) receptors are implicated in this process.

The headache pain of migraine seems to result from the activation of the trigeminalvascular system. The triggers to the development of migraine headache are probably chemical and are thought to originate in the brain, blood vessel walls and the blood itself. These triggers stimulate trigeminovascular axons causing pain and the release of vasoactive neuropeptides from perivascular axons. These neuropeptides act on mast cells, endothelial cells and platelets resulting in increased extracellular levels of arachidonate metabolites, amines, peptides and ions. These mediators and the resultant tissue injury lead to prolongation of pain and hyperalgesia.

Serotonin has also been specifically implicated in migraine. By activation of afferents, it causes a retrograde release of substance P. This is turn increases capillary permeability and oedema. In addition, magnesium has been suggested as having a role.

The complexity of the mechanisms involved in the genesis of migraine makes it likely that there are a number of ways to interrupt the processes to provide effective relief from migraine symptoms. A number of pharmacological agents and combinations of agents for the relief of migraine have been studied.

Therapeutics
Most patients who present to ED with severe migraine have tried to terminate their migraine headache with oral medication before their attendance. Therefore, this review will focus on the agents that are appropriate for use in ED. In considering them, the important issues to be considered are their efficacy, the need for additional medication and the incidence of "rebound" headache.

PROBLEMS WITH THE EVIDENCE
An evidence-based review of the therapeutics of acute migraine is compromised by the quality of the evidence available. With the exception of the drug company sponsored studies...
investigating the “triptans”, most studies are small with less than 50 patients in each subgroup being the norm. This means that the power of these studies to reach methodologically sound conclusions is limited. In addition, a variety of measures of “success of treatment” are used by different study groups, which makes comparison difficult. Given these limitations, this paper attempts to pull together the available evidence to inform practice and form a basis for further research.

PHENOTHIAZINES: CHLORPROMAZINE AND PROCHLORPERAZINE

Phenothiazines are antipsychotic drugs. In the central nervous system, they are powerful antagonists of the neurotransmitter action of dopamine in the basal ganglia and limbic system. They are also potent anti-emetics via effects on the chemoreceptor trigger zone and neuroleptic actions seem to change pain perception. In addition, they are α adrenergic antagonists (which can lead to orthostatic hypotension); chlorpromazine having greater α blocking effect than prochlorperazine. And they have anti-cholinergic properties and are antagonists at both histamine and 5-HT receptors.6

Besides its hypotensive effect, the major side effect of phenothiazines in short-term use is dystonia. This is an idiosyncratic reaction and may occur after a single dose.7 The mechanism by which phenothiazines act in migraine is uncertain. It is possibly the result of a combination of actions: anti-5-HT effects, anti-dopamine effect in the chemoreceptor trigger zone and vascular effects via its α blocking action.8

The evidence about chlorpromazine

Table 1 summarises the success rates with the use of chlorpromazine.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Patients (n)</th>
<th>Success rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lane et al65</td>
<td>1985</td>
<td>IV</td>
<td>52</td>
<td>94</td>
</tr>
<tr>
<td>Iserson62</td>
<td>1983</td>
<td>IM</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>McEwen63</td>
<td>1987</td>
<td>IM</td>
<td>36</td>
<td>47</td>
</tr>
<tr>
<td>Bell et al67</td>
<td>1990</td>
<td>IV</td>
<td>76 (3 arms)</td>
<td>89</td>
</tr>
<tr>
<td>Kelly68</td>
<td>1997</td>
<td>IV</td>
<td>42</td>
<td>95</td>
</tr>
</tbody>
</table>

The evidence about prochlorperazine

There are only a few small studies about prochlorperazine and migraine. Success rates of 67–92%68–70 have been reported. Most studies use a dose of 10 mg IV.

In comparative studies, prochlorperazine has been reported to give better pain relief than sumatriptan (one study),71 metoclopramide (two studies)72,73 and ketorolac (one study).74

A preliminary report regarding the use of rectal prochlorperazine suppositories reported good outcomes75 but its design makes evaluation difficult.

ERGOT ALKALOIDS

The pharmacological activity of ergot alkaloids derives from their ability to interact to varying degrees with subtypes of adrenergic, dopaminergic and tryptaminergic receptors.4 The ergot alkaloids have a number of side effects related to their pharmacological actions. These include peripheral vasoconstriction, peripheral gangrene, vomiting, nausea, chest pain, pruritus and headache.7

The ergot alkaloids seem to exert their antimigraine effect by strongly binding to 5-HT (Subtype 1B and 1D) receptors in the blood vessels of the dura and scalp resulting in inhibition of the trigeminal nerve mediated neurogenic inflammation.4 10–12

The evidence regarding DHE

Studies of DHE, either alone or in combination with metoclopramide or hydroxyzine, report success rates of 23%,13 73%17 and 93%18 when used in the dose of 1 mg IV.

In comparative studies, DHE has been shown to be more effective than pethidine (one study)20 or lignocaine (one study),14 less effective than chlorpromazine (one study)14 and of similar effectiveness to sumatriptan (one study)14 and pethidine (one study).20

Of particular note, in the only study where adverse events were carefully collected, 55% of patients treated with DHE experienced severe gastrointestinal side effects.14

Nasal sprays of DHE are also available. Headache relief rates of 27% at 30 minutes and 70% at four hours have been reported.19 One study suggests DHE spray to be less effective than sumatriptan subcutaneous (SC).21

HALOPERIDOL

Haloperidol is a butyrophenone, heterocyclic antipsychotic agent. It has effects on the chemoreceptor trigger zone reducing nausea and vomiting. It is an antagonist of the central effects of dopamine and is relatively selective for the D2 dopamine receptor. It is also a moderate α antagonist peripherally and has anti-5-HT effects. It is less sedating than chlorpromazine and results in less orthostatic hypotension. Dystonic reactions are haloperidol’s principal side effect.7 It is postulated that haloperidol is effective in migraine because of its anti-dopamine and/or anti 5-HT effects.

The evidence regarding haloperidol

No controlled or comparative trials of the use of haloperidol in migraine have been published.
Migraine: pharmacotherapy in the emergency department

243

V combined with central anti-dopamine effective than chlorpromazine (one study)14
studies lignocaine has been shown to be less effective than ketorolac (two studies).33 34 High dose metoclopramide (0.1 mg/kg/dose IV to a total of three doses; average dose 16 mg) was found to be of similar effectiveness to chlorpromazine (one study).18

The evidence about ketorolac
The doses used in studies have been 30–60 mg intramuscularly (IM). The reported success rate is 60%.33

In comparative studies, ketorolac (at a dose of 60 mg) has been reported to be less similar in effectiveness to pethidine (two studies)15 16 but at a dose of 30 mg IM was less effective than pethidine (one study).28 Ketorolac has been reported to be less effective than prochlorperazine (one study).25 A very small study compared ketorolac 60 mg IM with chlorpromazine 25 mg IV and found no difference in efficacy between the agents at two hours.37 However, important methodological problems make the value of this study questionable.

LIGNOCAINA
Lignocaine is a class 1b anti-arrhythmic agent (membrane stabiliser) used for the treatment of ventricular arrhythmia. It is also a potent local anaesthetic agent.9 It was hypothesised that lignocaine might act in migraine by its permeability.33

The evidence about lignocaine
The usual dose used in reported studies is of the order of 100 mg. A randomised, prospective, double blind trial comparing IV lignocaine (1 mg/kg) with placebo failed to demonstrate a difference between the two for the relief of the head pain of migraine.19 In comparative studies lignocaine has been shown to be less effective than chlorpromazine (one study)14 and DHE (one study).14

Recently, nasal lignocaine spray at a concentration of 4% has been trialled. A success rate of 55% has been reported however the early relapse rate was 42%.37

METOCLOPRAMIDE
Metoclopramide is a non-phenothiazine central dopamine antagonist and a peripheral muscarinic agonist. It increases gastric emptying and is anti-emetic at the chemoreceptor trigger zone.7 It is postulated that metoclopramide acts in migraine by anti-emetic effects combined with central anti-dopamine effects.38 Side effects of metoclopramide include drowsiness and dystonia.7

The evidence regarding metoclopramide
Uncontrolled studies have reported successful relief of migraine with metoclopramide of 75%.39 In a placebo controlled trail, metoclopramide 10 mg orally was found not to be superior to placebo in the relief of headache pain from migraine.40 However, studies of IV metoclopramide report benefit over placebo41 and in one a success rate of 67%.38

In comparative studies, metoclopramide in a dose of 10 mg IM or IV has been reported to be less effective than prochlorperazine (two studies).20 21 High dose metoclopramide (0.1 mg/kg/dose IV to a total of three doses; average dose 16 mg) was found to be of similar effectiveness to chlorpromazine (one study).18

PETHIDINE
Pethidine is a synthetic narcotic analgesic that exerts its pharmacological activity principally by binding to opioid receptors. The main side effects of pethidine are nausea and vomiting, respiratory depression, drowsiness and smooth muscle spasm, particularly in the biliary tree.9 A major concern with the use of pethidine is the possibility of development of dependence.9 This concern is supported by the findings of a study of 1900 sufferers of chronic headache, which found that 5% were narcotic abusers.12

It has been hypothesised that opioids are incapable of providing lasting, effective analgesia in migraine as they depend for their effect on serotonergic projections and patients suffering migraine have been shown to have central nervous system serotonin depletion.42

The evidence with respect to pethidine
The usual dose of pethidine is 75 mg IM/IV. A literature search covering the years 1976–1997 failed to identify any placebo controlled studies of the effectiveness of pethidine for the relief of migraine headache. Clinical success rates of 22% and 50% have been reported.16 28

In comparative trials pethidine, either alone or in combination with hydroxyzine and dimenhydrinate, has been reported to be less effective than DHE (one study)29 and chlorpromazine (one study)10 and of similar effectiveness to DHE (one study).29 With respect to ketorolac, pethidine was found to give better migraine relief than ketorolac in a dose of 30 mg IM (1 study)17 but when the ketorolac dose was 60 mg IM the agents had similar effectiveness (two studies).33 34

SUMATRIPTAN AND OTHER "TRIPTANS"
Sumatriptan is a specific and selective 5-HT (subtype 1D) agonist that has no effect on other 5-HT receptor subtypes. This receptor is found predominantly in cranial blood vessels and produces constriction of large blood vessels that may be dilated during episodes of migraine.44 Sumatriptan may be administered orally, SC or by nasal spray. Adverse effects include drowsiness, weakness, dizziness, flushing, rash, pruritis, increase in blood pressure,
chest pain or chest tightness. Importantly, sumatriptan is contraindicated in patients with a history of ischaemic heart disease, uncontrolled hypertension or the concomitant use of ergot preparations. There are also a significant number of non-responders for which no clinical, pharmacokinetic or genetic explanation has been found. The anti-migraine effect of sumatriptan is thought to be attributable to its effect on the 5-HT subtype 1D receptors in cranial blood vessels. Sumatriptan and ergot alkaloids block neurogenic inflammation by acting at pre-junctional 5-HT receptors on trigeminovascular fibres.

The evidence regarding “the triptans”

Three large double blind studies have compared the efficacy of sumatriptan in doses of either 6 mg or 8 mg subcutaneously with placebo. Clinical success rates were 70% and 75–80% respectively. In each study about half the sumatriptan treated group reported mild adverse effects including injection site reactions, nausea, flushing and chest heaviness. Thirty four to 60 per cent of patients successfully treated with sumatriptan reported recurrent headache within 24 hours. In comparative studies, sumatriptan when compared with DHE IV had a significantly higher rate of relief of headache at two hours, but there was no difference in rate of relief at three or four hours. Sumatriptan has reported to be more effective than DHE nasal spray. It has also been reported to be of similar effectiveness to chlorpromazine (one study) and less effective than prochlorperazine (one study). Sumatriptan treated patients reported a significantly higher rate of headache recurrence within 24 hours.

Newer “triptans” such as rizatriptan (10 mg orally) have reported success rates of the order of 75–80% and 70% respectively. In each study the number of non-responders for which no explanation has been found.

MAGNESIUM

In migraine patients, magnesium has been shown to play an important part as a regulator of neuronal excitability and therefore hypothetically of headache. Magnesium concentrations may also have effects on serotonin receptors, NMDA receptors and nitric oxide synthesis and release. Evidence suggests that about 50% of migraine sufferers have reduced concentrations of ionised magnesium.

The evidence about magnesium

A preliminary study reports clinical success in 35 of 40 patients after infusion of 1 g of magnesium sulphate. Response was more likely in those with low ionised magnesium concentrations.

Summary

Review of the evidence has some clear implications for the management of migraine in ED. Lignocaine fails to reach acceptable efficacy standards and as such is not recommended for use in acute migraine. Haloperidol and magnesium need to be studied in appropriate trials before conclusions can be drawn. Ketorolac, metoclopramide and pethidine perform a little better but each has been shown to be inferior to other treatments. The potential for dependence and abuse must also be considered with pethidine. The data on DHE are difficult to interpret because it is often used in combination with other agents, for example, metoclopramide, however it also has been shown to be less effective than chlorpromazine and sumatriptan in acute treatment and has a high rate of unpleasant side effects. At this time, the most effective agents seem to be prochlorperazine, chlorpromazine and sumatriptan, each of which have achieved greater than 70% efficacy in a number of studies.

Migraine: pharmacotherapy in the emergency department