Management of the acute migraine episode with sumatriptan vs. metoclopramide.

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SUMMARY.

**Background.** The pathophysiology of migraine remains unclear but the development of more specific drugs against migraine has revealed new insights into the structures and mechanisms involved. The efficacy of these new drugs varies among patients. In this study we assessed the efficacy of metoclopramide in comparison with sumatriptan to alleviate the acute phase of migraine.

**Hypothesis.** Metoclopramide is more effective than sumatriptan as migraine abortive therapy.

**Methods.** One hundred and twenty patients ranging from 18 to 65 years of age were divided at random into two groups. One group received 10 mg of metoclopramide (IV, three min), and the other group 6 mg of sumatriptan (subcutaneously, slowly). We registered the time course of pain decrease and the main secondary effects. Data were analyzed by $X^2$ with a significance level of $P<0.01$.

**Results.** The use of metoclopramide reduced the headache from level 3 to levels 0 or 1 in the first 15 min in 70% of the cases, while sumatriptan reduced the headache in only 58% of the patients. The autonomic symptoms associated with migraine (nausea and vomiting) respond better to metoclopramide. Furthermore, it has less secondary effects than sumatriptan.

**Conclusions.** In this study metoclopramide was more effective in alleviating the acute phase of migraine, and had less secondary effects than sumatriptan. *(Rev Biomed 2006; 17:175-182)*

**Key words:** Migraine, headache, metoclopramide, sumatriptan.

**Abbreviations:** IV, intravenous; EEG, electroencephalogram; SC, subcutaneous.
RESUMEN.
Manejo del ataque agudo de migraña con sumatriptan vs. metoclopramida.
Introducción. La fisiopatología de la migraña permanece aún poco clara, pero el desarrollo de fármacos más específicos contra la migraña ha revelado nuevos mecanismos y estructuras involucrados. La eficacia de estos nuevos fármacos varía entre pacientes. En este estudio evaluamos la eficacia de la metoclopramida en comparación con el sumatriptan para aliviar la fase aguda de la migraña.
Hipótesis. La metoclopramida es más eficaz que el sumatriptan para abortar un ataque agudo de migraña.
Método. 120 pacientes en un rango de edad de 18 a 65 años de edad fueron divididos aleatoriamente en 2 grupos. El primer grupo recibió 10 mg de metoclopramida (IV durante 3 min) y el otro grupo recibió 6 mg de sumatriptan (subcutánea, lentamente). Se registró el curso temporal de la disminución de la cefalea y los principales efectos secundarios. Los datos fueron analizados mediante $X^2$ con un nivel de significancia de $P < 0.01$.
Resultados. El uso de la metoclopramida reduce la cefalea de nivel 3 a niveles 1 o cero en los primeros 15 min en 70% de los pacientes, en tanto que el sumatriptan reduce el dolor sólo en 58%. Los síntomas autonómicos asociados a la migraña (náusea y vómito) respondieron mejor a la metoclopramida. Además, presentó menos efectos secundarios que el sumatriptan.
Conclusiones. En este estudio, la metoclopramida fue más efectiva en aliviar la fase aguda de la migraña y tiene menos efectos secundarios que el sumatriptan. (Rev Biomed 2006; 17:175-182)
Palabras clave: Migraña, cefalea, metoclopramida, sumatriptan.

INTRODUCTION.
The pathophysiology of migraine remained obscure for a long time, but during the last decade, the development of new drugs as well as the use of others that are not so new, and the application of new techniques of neurophysiological evaluation (e.g., magnetic transcranial stimulation), started to reveal the structures and underlying mechanisms of migraine (1). Studies suggest that the aura preceding an acute migraine attack can be produced by neuronal depolarization resembling the spreading depression of Leao and/or change in blood flow rate (2-4). Other findings strongly support the involvement of genetic factors in the development of migraine (5). The susceptibility to migraine is based on cortical hyper-excitability. There are various factors contributing to this hyperexcitability such as anomalies in the performance and number of P/Q calcium channels, alterations in mitochondrial metabolism, and hypomagnesemia (3, 5-7). Hypomagnesemia by itself produces alterations in mitochondrial metabolism, modifies neuronal polarity, and can influence the release of neurotransmitters of excitatory or serotonergic systems (8). However, the mechanisms that relate neuronal depolarization with the metabolic changes that peak in an acute migraine attack are yet unknown.
Pharmacological, pathophysiological, and genetic evidence has revealed the participation of the nigro-striatal system in pain, nausea, and vomiting present in migraine (9). Metoclopramide has been used for long time as a prokinetic agent and against nausea and vomiting because of its antidopaminergic effects (D$_2$ antagonism). The use of dopaminergic antagonists has been effective to abort migraine (10-13). It is known that the substance nigra (pars reticulata) has an important role in directing electrical activity either back to the striatum or to the output structures of the basal ganglia (thalamus, superior colliculus, brain stem) and that it plays an important role in controlling epileptic crises (14). In some instances, migraine is the aura of an epileptic crisis or cephalea is a postictal event, or even a migraine attack may trigger the seizure (migralepsy) (15). This suggests that it may be the same route that is excited by the spread of the depolarization (16), regardless whether it is
Sumatriptan vs metoclopramide in migraine

Sumatriptan is a serotoninergic HT-1B/1D agonist developed at the beginning of the 90’s. However, it has more effect on the 1D receptors than on the 1B, which explains its minor central effect. These receptors participate in the decrease of central serotonin and can normalize the changes in frequency spectrum of the electroencephalogram (EEG) that accompanies the headache induced by nitroglycerine. These receptors can be pre-(self-receptors) or post-synaptic and are found in the mid brain and the raphe nucleus (17).

In this study we evaluated the efficacy of a new drug (sumatriptan) vs. an old one (metoclopramide) in reducing the level of pain of an acute migraine attack.

MATERIAL AND METHODS.

The study was performed between September 1997 and March 2000. A total of 3,124 patients with the diagnosis of acute cephalae attended the Neurology Out-Patient Department and Emergency Room of the Central Military Hospital. Of this group of patients, 120 fulfilled the International Headache Society criteria for migraine (1.1; 1.2) (18) and were randomized to one or the other study group, according to the following criteria: patients 18 to 65 years of age, of either sex, with intensity from moderate to severe, without aura (1.1) or with aura (1.2) (18), without restriction in time of evolution of the migraine and history of one to six attacks in one month. Patients with fever prior to the onset of pain, pregnancy, use of psychotropic drugs, tobacco or alcohol in the last 24 hours, recent trauma, meningism, or three months previous use of drugs (antihypertensive, antiparkinsonian, antihistamine, barbiturate, anticholinergic) and for conditions such as coronary disease and morbid obesity were excluded from the study.

Once patients were apprised of the procedure to be followed, and after providing informed consent, they were located in a dark room, and were asked to rank their own headache at that moment and subsequently, according to the headache intensity scale, with the following criteria: 0 = no headache; 1 = mild headache; 2 = moderate headache; 3 = intense headache; in addition to the transfer associated symptoms at that moment. Headache progress after administration of one of the two drugs was evaluated every 15 minutes, for an hour, using the same scale. Vital signs were measured both at the beginning and at the end of the study.

The metoclopramide group received 10 mg IV (Carnotprim, lot No. B-5510108), slowly delivered in 3-5 minutes. This presentation was selected because of its high bioavailability and low cost. The sumatriptan group received 6 mg subcutaneously (Inmigran, B-0289FFA), again, slowly. These doses and routes were selected, because they have the best pharmacokinetic profile, clinical efficacy, and less secondary effects (20-21). Results were statistically analyzed by $\chi^2$ test with a significance of $P<0.01$.

RESULTS.

A total of 120 patients were included and assigned by random tables to the metoclopramide or sumatriptan group. One hundred and eleven patients were women (92.5%), while 9 were men (7.5%). The greater incidence of migraine in women reported by other authors was corroborated (22, 23). Table 1 shows the frequency by age groups, with the highest frequency being in young patients, followed by patients in the third and fourth decades. However, the reported ranges vary considerably (22, 23) as the natural history of the disease is one of remissions and exacerbations, with possible reappearance in advanced age, after decades of remission.

Of the 60 patients who received metoclopramide, 51 (85%) reported level 3 headache and 9 (15%) level 2 headache at first (table 2). Fifteen minutes after metoclopramide administration, 33 patients (55%) experienced headache relief to level 0, while in 9 patients (15%) the headache was reduced to level 1; thirty minutes after metoclopramide administration, 39...
patients (65%) reached level 0, and 11 patients (18.3%) reported level 1; forty five minutes after, 47 patients (78.3%) improved to level 0, and 4 (6%) presented level 1 headache; sixty minutes after treatment, the headache in 54 patients (90%) had resolved, and only six patients (10%) had a level 1 headache (figures 1, 2).

Of the patients treated with sumatriptan, 55 (91.6%) had level 3 headache, and 5 (8.3%) reported level 2 headache (table 3). Fifteen minutes after the sumatripan injection, 35 patients (58%) reported a decrease to level 1 (figure 1). However, none of the patients reported relief of the headache to level 0 (figure 2 and table 3). Thirty minutes after administration, 34 patients (56%) reported no headache and 12 patients (20%) had reached level 1, 10 patients (16.6%) reported level 2 headache and 4 patients (6.6%) reported no change in the initial level 3 headache. Forty-five minutes after drug delivery, the number of patients with headache relief (level 0) increased to 45 (75%), 6 patients (10%) stated level 1 headache; 7 patients (11.6%) reported level 2; and 2 patients (3.3%) still had level 3 headache. Sixty minutes after administration, the number of patients with level 0 headache increased to 47 (78%); while 7 patients

Table 1. Number of patients with migraine by age group.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>61</td>
<td>50.83</td>
</tr>
<tr>
<td>31-40</td>
<td>33</td>
<td>27.5</td>
</tr>
<tr>
<td>41-50</td>
<td>15</td>
<td>12.5</td>
</tr>
<tr>
<td>51-65</td>
<td>11</td>
<td>9.17</td>
</tr>
<tr>
<td>Total of patients</td>
<td>120</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2. Graduation and evolution of headache after metoclopramide administration.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Headache intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>45</td>
<td>47</td>
</tr>
<tr>
<td>60</td>
<td>54</td>
</tr>
</tbody>
</table>

Figure 1.- Temporary course of the effect of metoclopramide and sumatriptan administration on level 3 headache. The number of patients reporting a reduction of the headache to level 0 or 1 during the four studied intervals was added. The difference is only significant for the first 15 min of effect P<0.01.
(11.6%) reported level 1 headache; 5 patients (8.3%) remained with level 2 headache and 1 patient (1.6%) experienced no headache relief.

The difference in pain-relieving efficacy between the two drugs was statistically significant (P<0.01) only at fifteen minutes after drug administration (figure 1, 2). The most frequently reported secondary effects were dizziness and drowsiness for metoclopramide, but never lasting more than twenty minutes. For sumatriptan, the most frequently reported adverse effect, and one with great impact on the patients, was the momentary increase of the headache, mainly in the frontal region, followed in order of importance by shortness of breath, thoracic or neck discomfort (pressure sensation), anxiety, fatigue, pain at the injection site, sweating, sensation of heat, and paresthesias of variable duration, although none of the side effects lasted more than forty minutes. With the use of either of the two drugs, the vital signs of the patients remained stable during the period of observation (not shown).

**DISCUSSION.**

Cephalea is a very common problem in emergency rooms, and the therapy options are not always satisfactory. Ergotamine was the only specific antimigraine-drug until 1993, when tryptan was first employed (24), and was later followed by dopamine receptor antagonists (25), non steroidal drugs (26) and steroids (27). Despite all these treatments against migraine attack none
of the individual drugs or combinations of them are totally effective. And the persistence of pain, the recurrence within the next 24 h, secondary effects, and high cost are common. This makes the management of these patients difficult.

The difference observed between metoclopramide and sumatriptan in headache relief can be explained by different factors. One of them can be related to the administration route and bio-availability of these drugs. The intravenous route of metoclopramide administration affords greater bio-availability than the subcutaneous route used for sumatripan (20), as it arrives to the action site faster. Furthermore, sumatriptan has a greater effect on the 5-HT/1D receptors, which are not as abundant in the central nervous system as the 5-HT/1B type (28). Another factor that must be considered under present conditions is that the drugs employed have different power, and which was not normalized. In spite of the foregoing, the decrease of the level 3 headache to levels 0 or 1 by the action of metoclopramide in the first fifteen minutes (42 patients out of 51) is better than the effect of sumatriptan (35 patients out of 55), and is statistically significant ($P<0.01$). Results after 60 minutes show that the beneficial effect of metoclopramide is global, while with sumatriptan some patients were still suffering from intense headache (levels 2 or 3), although these differences are not statistically significant ($P>0.01$). This lack of statistical significance could be due to two factors, one of them being the small sample size in the series, which rendered the statistical test non significant, although, as can be seen, all patients were free of headache and, in this sense, metoclopramide represents a better option. The other factor is the different mechanisms of action, although it is incompletely understood, metoclopramide is considered a neuroleptic drug, and is known for its D$_2$ antagonism (dopamine,-receptors) effects (29). D2 receptors are found in large quantities in the nigro-striatal system, and the mesolimbic and tuberoinfundibular region. The presence of dopaminergic self-receptors has been described in the nigro-striatal and mesolimbic regions (30), therefore, the action of metoclopramide can be pre-or post-synaptic. It also binds to 5-HT$_{3A}$ subfamily receptors (potent antagonist property) and 5-HT$_4$ agonists (31, 32), and these are localized in the area postrema in the central nervous system and play a key role in the nausea and emesis physiology, which explains the better relief of nausea and vomiting observed with metoclopramide (29). Metoclopramide appears to increase the sensitivity of the tissues to acetylcholine, a chemical messenger, and its participation as an active metabolite can not be ruled out (33). While sumatriptan has effect only on 5-HT 1B/1D receptors and although a pharmacological action at 5-HT$_1F$ receptors has not been excluded (34), these receptors are found distributed in vessels of the dura mater and cortico-pial vessels, belonging to the trigeminal o-vascular system (35), and apparently this is the route that conducts the pain. However, the exact site of action of this type of drugs is still under discussion.

The most frequently reported secondary effects for metoclopramide were dizziness and drowsiness. However, these are often considered beneficial by the patients, because they decrease anxiety, and furthermore very few patients reported them. Sumatriptan, on the other hand, has many secondary effects that troubled patients, and this makes it less advantageous. One of the most important secondary effects was the mild increase of the headache; the other is a “thoracic” effect, translated as anxiety or shortness of breath, which has also been reported by other authors as common for the subcutaneous route (41%) (35, 36).

Whether the shortness of breath sensation is due to anxiety or is actually secondary to a bronchospasm is yet unknown, but it would be interesting to understand the phenomenon, and it must be monitored when prescribing sumatriptan. Although a significant association between sumatripan use and coronary artery spasm has not been found yet, reports of thoracic pain, infarction and coronary vessel spasm continue to appear in
Recent studies report that new formulations and administration routes (rectal and nasal) of sumatriptan are more effective, since they offer better bio-availability. However, they have only been compared against sumatriptan or dihydroergotamine or another tryptans (28, 37), and therefore must yet be compared against metoclopramide.

In short, though the differences in the intravenous vs subcutaneous administration route and in bio-availability are important barriers to compare metoclopramide against sumatriptan in the treatment of the acute migraine episode, the simple fact of greater speed of action, autonomic symptom relief, fewer side effects, and the very large difference in cost, make metoclopramide a more effective drug for treating patients suffering from acute migraine. The use of metoclopramide during pregnancy appears to be safe, but more studies are needed to confirm these results (38). Other administration routes are possible for both drugs. Metoclopramide can be applied by intramuscular injection and sumatriptan can be delivered by intranasal route. Comparison of these drugs and administration routes can increase the therapeutic options to relieve the acute migraine attack.

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