

Evaluation of medical prescriptions containing associations with antidepressants in a manipulation pharmacy

Avaliação de prescrições médicas contendo associações com antidepressivos para tratamento da enxaqueca em uma farmácia de manipulação

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RESUMO

O objetivo do trabalho foi determinar e avaliar o perfil dos medicamentos prescritos para a patologia, de acordo com protocolos clínicos conhecidos, referentes ao risco-benefício inerente a estes diante da gama de opções terapêuticas existentes e da falta de tratamento específico. Foi avaliado o perfil das prescrições destinadas ao tratamento da enxaqueca, dispensadas numa farmácia de manipulação de Teresina, Piauí, no período de 2 de janeiro à 2 de junho de 2012. Foram avaliadas 121 prescrições e todas continham medidas profiláticas em detrimento do tratamento de suspensão das crises. Destas, 56,51% continham nortriptilina (de 5 a 40 mg), com a associação de flunarizina e atenolol a mais frequente, 36,36% continham amitriptilina (de 10 a 75mg), e a associação com os betabloqueadores, propranolol ou atenolol, a mais frequente, e por fim, evidenciado a influência da flunarizina, esta também foi avaliada, com 7,43% das prescrições. Apesar de pouco frequente, destacam-se as associações com *Ginkgo biloba* e vitamina B6, cuja comprovação terapêutica não foi ainda completamente elucidada. A grande representatividade de medicamentos profiláticos na terapia da enxaqueca em Teresina, Piauí, sendo os antidepressivos tricíclicos, amitriptilina e nortriptilina, seguido do bloqueador de canal de Ca²⁺, flunarizina, os medicamentos de primeira escolha dos prescritores locais.

Palavras-chave: Transtornos de enxaqueca; Antidepressivos; Prescrições de medicamentos; Farmacologia clínica.

ABSTRACT

The aim of this work was to determine and evaluate the profile of prescription drugs to this pathology, regarding the risk-benefit inherent in these given the range of therapeutic options and lack of specific treatment. Was evaluated the profile of prescriptions to migraine treatment dispensed in a manipulation pharmacy from Teresina, Piauí, in the period from January 2 to June 2, 2012. 121 prescriptions were evaluated and all were based on prophylactic measures, not in suspension of crises. Of these, 56.51% contained nortriptyline (from 5 to 40 mg), being the association with flunarizine and atenolol the most frequent. 36.36% contained amitriptyline (10 to 75mg) and the association with beta-blockers (propranolol or atenolol) the most frequent. Finally, because of flunarizine influence, this was also evaluated, represented by 7.43% of the prescriptions. Although unusual, was noteworthy the associations with *Ginkgo biloba* and vitamin B6, whose therapeutic evidence has not yet been fully elucidated. There is a great representativity of prophylactic drugs in prescriptions from a manipulation pharmacy from Teresina, Piauí, with the tricyclic antidepressants, amitriptyline and nortriptyline, followed by the calcium channel blocker, flunarizine, the first-line drugs in the choice of local prescribers.

Keywords: Migraine disorders; Antidepressive agents; Drug Prescriptions; Clinical pharmacology.

INTRODUCTION

According to the Brazilian Society for Neuroscience, the headache is one of the most frequent complaints. It is estimated that 85% of the world population has already suffered by this pain, with a prevalence estimated in 15%, being more common in women (14-20%) than men (4-10%) (KRYMCHANTOWSKY & SILVA, 2005). As a chronic illness, is characterized by repetitive and lasting episodes of headaches, being one of the most frequent causes of medical assistance in general or specialty clinics (HAMERSCHLAK & MATOS, 2008).

Migraine is currently defined as a primary disease of the brain with a neurovascular component. It is clinically characterized by attacks of pain, usually of high intensity, which last between 4 and 72 hours, followed by autonomic dysfunction (nausea and vomiting), as well as increased sensitivity to light, sounds and smells (HAMERSCHLAK & MATOS, 2008).

As a crucial factor in the onset of migraine, stands out in the international scientific community the theory of "Spreading Depression of Lion" (DA), referring to an event characterized by successive neuronal electrical discharge, initially in the cortex, resulting from physical or emotional stress, hormonal changes (use of contraceptive pills, menstruation), food, hypoglycemia, strong odors and many others. These discharges are distributed giving rise to a succession of events, initially release of neurotransmitters in the brain vessels resulting in the neurogenic inflammation, followed by cerebral vasodilatation, probably the cause of pain, and stimulus propagation to the trigeminovascular nucleus, producing autonomic actions. This effect characterizes the pathophysiology of the disease (VINCENT, 1997; NASCIMENTO, 2008).

When the patient has more than one migraine per month, or if the crisis is extremely severe and long-lasting (2-3 days) even at low frequency it is preferable the preventive treatment, otherwise it is preferable the pain treatment (SANVITO & OLIVEIRA, 1993). In the first case the therapy consists in use of triptans and ergot alkaloids, what represents the drugs of first line in most patients. In the second case, it is preferred the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and in cases of refractoriness, neuroleptic drugs from the opioid class are chosen because your increased intensity (BIGAL, BORDINI & SPECIALI, 1999; SCHMIDT & SCHMIDT, 2000).

The preventive medications avoids the debilitating pain inherent in the clinical situation

that hinders daily activities. Moreover prevents the emergence of chronic headache induced by analgesics (PINTO et al., 2009). For prophylactic medications still exists the β -blockers (propranolol, metoprolol, timolol), tricyclic antidepressant (amitriptyline) and the anticonvulsant (valproic acid). The latter should be used with caution in pregnant women since it may cause fetal malformation (LINDE & ROSSNAGEL, 2006). There is also some evidence that methysergide and pizotifen, serotonin antagonists drugs, can be used as prophylactic drugs (KRYMCHANTOWSKY & FILHO, 1999; MOJA et al., 2005).

The range of therapeutic options available, the lack of definitive knowledge about the disease and the variability of responses for each patient, leads to the neurologist to the arduous task of evaluate which the best drugs for each of your patients. Considering these factors the treatments most often found in prescriptions become a representation of the medical observations of effective practical cases.

In this view added to the expressive number of prescriptions for the migraine treatment in a manipulation pharmacy in Teresina - PI, including the presence of unusual drugs without recommendations in regular literature, leads to the aim of this research in evaluate the profile of medications and association more prescribed in Teresina-PI. This research includes the analyses of doses and risk-benefit related.

MATERIALS AND METHODS

A quantitative sampling study with qualitative emphasis was developed which were collected all prescriptions written by neurologists whose purpose was the treatment of migraine. These data were obtained from the computerized system "Fórmula Certa[®] 5.5", from a manipulation pharmacy in Teresina - Piauí in the period from January 2 to June 2, 2012 (5 months). The study was approved by the Research Ethics Committee under protocol number of CAEE: 0424.0.045.00-11.

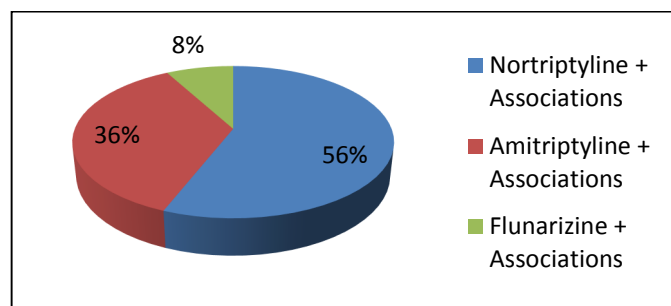
According to clinical protocols for the migraine treatment (BRUNTON, LAZO & PARKER, 2006) the antidepressants, amitriptyline and nortriptyline and the blocker of calcium channel, flunarizine, were selected for analysis of sales profile, associations and dosages commonly prescribed and their adaptations according to specific scientific literature.

RESULTS AND DISCUSSION

After sampling were found 121

prescriptions with drugs or associations of drugs for migraine treatment. All these prescriptions have included prophylactic drugs. Among the various classes of drugs indicated for this purpose, the representatives of tricyclic antidepressants and blockers of calcium channel were found in higher proportions. A proportion of 56% had nortriptyline as a single constituent or in associations, 36% had amitriptyline in the same conditions, and 8% had flunarizine, as shown in figure 1. Beside these was found in association with them, beta-blockers, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and others classes, as showed in table 1.

Figure 1 – Schematic representation of the most prescribed drugs for migraine prophylaxis, found in prescriptions dispensed in a manipulation pharmacy in Teresina-PI.



Source: Direct research conducted in the period from January 2 to June 2, 2012.

In table 1 besides the drugs is possible to observe the commonly prescribed dosages and compare them with doses recommended by clinical protocols referred by Krymchantowsky & Filho (1999), Moreira & Silberstein (2004), GherPELLI (2002) e Chhateretal., (2009).

The most common associations are observed in subsequent tables where those containing amitriptyline, nortriptyline, and flunarizine were referenced in Tables 2, 3 and 4 respectively. For prescriptions with nortriptyline the most frequent association has included flunarizine and atenolol, representing 42.65% of its total. For those containing amitriptyline the most frequent association has included a beta-blockers, propranolol or atenolol, representing 31.82% of its total. Finally the prescriptions containing flunarizine showed no significant frequency however it is worth noting the association with pyridoxine (vitamin B6) and with the herbal *Ginkgo biloba*.

The references show that to the prophylactic treatment of migraine the amitriptyline could be used in dosages of 25 to 75 mg, below than doses used to depressant treatment (50 to 300 mg by the day). The dosage of nortriptyline for migraine was not found, however for depression

treatment is referenced between 30 and 200 mg by the day (GHERPELLI, 2002; FLOREZ, ARMIJO & MEDIAVILLA, 1997). Therefore, as well as amitriptyline, nortriptyline should be used in smaller dose or near to the lower limit of antidepressant treatment recommended dosages. Therefore the prescriptions analyzed were in accordance with the recommended doses with 10-75 mg for amitriptyline and 5-40 mg for nortriptyline.

Nortriptyline has less sedative effect than amitriptyline, but several scientific studies have demonstrated the superiority of results with the use of amitriptyline (AQUINO & FORTES, 2009). In disagree with that, the analysis of prescriptions dispensed in Teresina shows a preference for nortriptyline by local prescriptors.

The indicated dosage for Flunarizine in the treatment of migraine is 2.5 to 10 mg by day and the dosages found were also within this range (GHERPELLI, 2002; FLOREZ, ARMIJO & MEDIAVILLA, 1997). In general, all prescriptions have drugs with dosages in accordance with those recommended in literature.

The tricyclic antidepressants for acting in 5HT_{1D/1B} receptors on presynaptic nerves inhibit the release of vasodilator peptides discussed above, thereby reducing the production of neurogenic inflammation and consequent production of pain. Thus

Thus its use is justified as a prophylactic agent, reducing the release of substances responsible for pain in the next trigger event in the depression spreading (BRUNTON, LAZO & PARKER, 2006; MOREIRA & SILBERSTEIN, 2004).

Moreover these antidepressants are also anxiolytics agents being useful in cases of migraine associated with stress, restlessness, and insomnia, resulting in a slight sedation and inhibiting the triggering stimuli of crisis (BRUNTON, LAZO & PARKER, 2006).

As amitriptyline has greater sedative effects than nortriptyline, it justifies his great preference for prescribers in the region. However it is important to considerate that their choice should take into count the lifestyle, work and studies routine of their patients.

In addition to antidepressants there was also a huge variation in amount of prescribed substances as showed in table 2. As an example has the beta-blockers, among them, those used with proven efficacy for migraine are propranolol (which is also the oldest used to prevent migraines) and atenolol, that must be administered in increasing doses until optimization of the dose/effect for each individual patient. The most

frequent side effects are fatigue, depression and memory disorders, sexual impotence, reduced tolerance for exercise, bradycardia and hypotension, negative influences on glucose metabolism and cholesterol, etc. (KRYMCHANTOWSKY & FILHO, 1999).

Regarding to NSAIDs despite the most notable action is in the acute treatment, some also show utility in preventive treatment, such as aspirin, indomethacin, fenoprofen, naproxen sodium and tolfenamic acid, especially in some specific periods, such as the pre and post menstrual (SANVITO & MONZILLO, 1997). Among the NSAIDs prescribed was not found those listed above what suggests the use of them only in acute symptoms.

It is noteworthy that, although to be in a lesser extent, medical indications of not conventionally drugs applied for migraine occurs, such as pyridoxine and *Ginkgo biloba*. A clinical and pharmacological test with extracts of *Ginkgo biloba* demonstrates its therapeutic action on the typical migraine with aura. This effect is mainly related to its terpene fraction, concentrated in Ginkgolideos B. This is a natural modulator of glutamate in the central nervous system and moreover is a potent negative regulator of platelet activating factor (PAF), a potent pro-inflammatory agent released from platelets and leukocytes during the first phase of the migraine attack, which can sensitize the trigeminal vascular nerves and promote pain (D'ANDREA et al., 2009). However, despite inferences and theories, the mechanism of action is not fully understood, nor is plausible for all types of migraines, requiring further studies to become trusted (CHHATER et al., 2009).

Vitamin B6 (pyridoxine) has been used to prevent migraine headaches, particularly related to menstruation. Its usual dose is 50 to 400 mg by day. Its pharmacological effect is not fully understood however their use could be justified because your influence in histamine production, a hormone responsible to controlling the infections and which can be produced in response to stress, an important cause of migraine (PIPER & COLLAGES, 1997).

Compared to conventionally accepted treatments whose mechanisms are also not fully elucidated and whose benefits vary in relation to the patient, these unusual medicines may also have their use justified. It should be only followed about progressions of each patient to assess the effectiveness of treatment.

Finally the prescriptions without antidepressants, representing 8% showed the second most commonly prescribed class for associations, the flunarizine (Calcium channel

blocker). Its use in migraine is explained for been more easily penetrable in blood-brain barrier than others calcium channel blockers. Besides, its action is related to inhibition of neuronal electrical discharges, probably by inhibiting the emergence of the phenomenon of DA, which would avoid recurrence of seizures (BRUNTON et al., 2006; KRYMCHANTOWSKY & FILHO, 1999).

CONCLUSIONS

Thus although there is no rule in the effectiveness of migraine treatment, dependent mainly of variables related to the patient, was noticed a trend in drugs prescribed by neurologists in Teresina, with a prevalence of tricyclic antidepressants followed by the calcium channel blocker, previously described. Both classes, by having potential inhibitory effect in triggering of migraine, have theoretical background to be the drugs main prescribed for migraine prophylaxis.

However, these professionals should take into account the lack of studies consolidated for using unconventional drugs such as *Ginkgo biloba* and *Vitamin B6*, whose benefits are referenced but not fully elucidated, not knowing the long term effects or even therapeutic dosage with efficacy and safety. Thus it is necessary to use them with caution and offer a targeted monitoring of these patients.

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Table 1 - Class of drugs and their dosages prescribed for the treatment of migraine in a manipulation pharmacy from Teresina.

Drug	Class of Drug	Doses found in the prescriptions analyzed	Recommended daily dosage for migraines
Amitriptyline	Tricyclic Antidepressant	10 -75 mg	25 a 75 mg
Nortriptyline	Tricyclic Antidepressant	5 – 40 mg	--
Flunarizine	Ca ⁺⁺ Channel Blockers	2,5 – 10 mg	2,5 - 10 mg
Propranolol	Beta- Blockers	20 - 80 mg	40 – 180 mg
Atenolol	Beta- Blockers	10 – 100 mg	50 – 120 mg
Pyridoxine	Vitamin B ₆	100 – 450 mg	50 – 400 mg
Nimesulide	NSAIDs	50 mg	50 – 200 mg
Meloxicam	NSAIDs	7,5 – 15 mg	5 - 15 mg
Paracetamol	NSAIDs	300 – 500 mg	500 – 1500 mg
Piracetam	NSAIDs	500 mg	500 mg – 12 g
Tenoxicam	NSAIDs	15 mg	10 - 20 mg
<i>Ginkgo biloba</i>	Herbal	120 mg	120 – 240 mg

Source: Direct research conducted in the period from January 2 to June 2, 2012.

Table 2 - Drugs association containing nortriptyline prescribed for the treatment of migraine in a manipulation pharmacy from Teresina.

Drug 1	Drug 2	Drug 3	Drug 4	Prescriptions (n°)	Prescriptions (%)
Nortriptyline	-	-	-	16	23,53
Nortriptyline	Atenolol	-	-	8	11,76
Nortriptyline	Flunarizine	-	-	2	2,94
Nortriptyline	Flunarizine	Atenolol	-	29	42,65
Nortriptyline	Atenolol	Pyridoxine	-	6	8,82
Nortriptyline	Flunarizine	Atenolol	Pyridoxine	5	7,36
Nortriptyline	Flunarizine	Atenolol	<i>Ginkgo biloba</i>	2	2,94
Total				68	100

Source: Direct research conducted in the period from January 2 to June 2, 2012.

Table 3 - Drugs association containing amitriptyline prescribed for the treatment of migraine in a manipulation pharmacy from Teresina.

Drug 1	Drug 2	Drug 3	Drug 4	Prescriptions (n°)	Prescriptions (%)
Amitriptyline	-	-		10	22,72
Amitriptyline	Propranolol	-		7	15,91
Amitriptyline	Flunarizine	-		5	11,36
Amitriptyline	Atenolol	-		7	15,91
Amitriptyline	Pyridoxine	-		2	4,55
Amitriptyline	Nimesulide	Famotidine		2	4,55
Amitriptyline	Meloxicam	Paracetamol		2	4,55
Amitriptyline	Paracetamol	-		2	4,55
Amitriptyline	Atenolol	Flunarizine		3	6,81
Amitriptyline	Paracetamol	Famotidine	Meloxicam	1	2,27
Amitriptyline	Propranolol	Flunarizine	-	2	4,55
Amitriptyline	Tenoxicam	-	-	1	2,27
Total				44	100

Source: Direct research conducted in the period from January 2 to June 2, 2012.

Table 4 - Drugs association containing flunarizine prescribed for the treatment of migraine in a manipulation pharmacy from Teresina.

Drug 1	Drug 2	Drug 3	Drug 4	Prescriptions (n°)	Prescriptions (%)
Flunarizine	Pyridoxine	-	-	4	44,44
Flunarizine	Piracetan	<i>Ginkgo biloba</i>	-	1	11,12
Flunarizine	Atenolol	-	-	4	44,44
Total				9	100

Source: Direct research conducted in the period from January 2 to June 2, 2012.