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TREXIMET® (SUMATRIPTAN AND NAPROXEN): THE FIRST COMBINATION TRIPTAN/ NSAID FOR ACUTE MIGRAINE

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Headache is a common complaint in the United States. Up to 20% of the adult population suffers from primary headache.[1] These numbers may not reflect the true patient population because many headache sufferers never seek diagnostic treatment. "Primary headache" is a broad term which encompasses migraine, cluster, tension, and miscellaneous headaches. Migraines are differentiated by disability, nausea, and photophobia.[2] Costs associated with alleviating migraine reach nearly 17 billion dollars each year.[3]

Acute migraine treatment incorporates several drug classes including NSAIDs, triptans, and ergotamines. Current first line therapy is the use of NSAIDs, including naproxen and effervescent aspirin.[4] Triptans and ergotamines are often used after NSAID treatment has failed.

In April 2008, the Food and Drug Administration (FDA) approved the first triptan/NSAID combination pill for the acute treatment of migraine: sumatriptan/naproxen (Treximet®). This article will review the pathophysiology of migraine, pharmacological properties, results of two clinical trials, and adverse events of sumatriptan and naproxen.

PATHOPHYSIOLOGY OF MIGRAINE

The pathophysiology involved in migraines have been widely debated. Migraine recurrence may be an inherited or acquired defect in the trigeminocervical CNS system. Inappropriate activation of the trigeminocervical system may explain migraines associated with aura and the menstrual cycle, while both exogenous and endogenous triggers may result in migraine in individuals with lowered activation thresholds.[5]

The pathway of trigemino-cerebrovascular involvement starts with the trigeminal nerve. The first branch innervates intracranial vessels and the meninges via sensory nerve fibers. The pathway extends through secondary neurons in the brainstem through the trigeminal nucleus caudialis to the trigeminocervical complex. From here, the cortical areas are activated, leading to pain perception.[1]

Once the migraine threshold is reached, the dorsal raphe releases both norepinephrine and serotonin.[6] Vasodilation occurs and vomiting centers are activated. Vasodilation brought on by the release of norepinephrine and serotonin is further enhanced by trigeminal activation of cortical areas, which release neurokinin A, substance P, and calcitonin gene-related peptide (CGRP).[6]

CGRP, a vasodilator, is thought to play an integral role in migraine pathophysiology. The trigeminal nerve ganglion contains many CGRP-containing nerves. CGRP is released after vasocon-

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striction in order to restore vascular tone. Additionally, CGRP is elevated in acute migraine attack, and decreased after treatment with a triptan.[1,7]

An inflammatory component may also play a role in migraine pathophysiology. Prostaglandins may make pain worse by attentuating the inflammatory response.[8]

PHARMACOLOGY

The combination pill of sumatriptan and naproxen contains sumatriptan succinate, a member of the triptan class, and naproxen sodium, an NSAID.

The 5-$HT_{1B/1D}$ agonists, known as the "triptans," help regulate CGRP levels. Their mechanism of action is thought to be through 5-HT_{1B} receptor mediated vasoconstriction of cerebral vessels in the smooth muscle layers of the meninges and cerebral arteries. A second mechanism of action may occur through presynaptic trigeminal nerve receptors to inhibit the release of GCRP, thus inhibiting vasodilation mediated by the neuropeptide.[1] All triptans appear to have similar safety and efficacy profiles.[4]

Naproxen is an NSAID that works as an analgesic and antipyretic in addition to having anti-inflammatory properties. Naproxen inhibits both COX-1 and COX-2 enzymes. Studies have shown that NSAIDs may be as effective as the triptans in aborting acute migraine.[3]

CLINICAL TRIALS

Brandes, et al. conducted two identical phase 3, randomized double-blind, parallel group, controlled clinical studies comparing the effectiveness and safety of sumatriptan and naproxen as a combination versus either agent alone or placebo in the treatment of acute migraine attack.[8] Inclusion and exclusion criteria for the two trials were identical. The only difference between the two studies were the estimated enrollment numbers (estimated enrollment for Study 1 was 1200 patients, estimated enrollment for Study 2 was 1400 patients; actual enrollment for Study 1 was 1461 patients, actual enrollment for Study 2 was 1495 patients).[8]

The investigators used primary outcomes of relief of headache 2 hours after dosing and absence of photophobia, phonophobia, and nausea to evaluate the efficacy of the combination treatment versus placebo. They employed sustained, pain-free response as a primary outcome measure against each monotherapy. Secondary endpoints analyzed were sustained pain relief after 24 hours and sustained relied of photophobia, phonophobia, and nausea.[8]

Table 1: Clinical Trials Summary[3,8,10]

		Treximet®	Sumatriptan 85mg	Naproxen 500mg	Placebo	p value (vs. placebo)	p value (vs. sumatriptan)
Results from Landy, et al.[3]							
Return to Function (median time)	Study 1	4h	4h	7h	11h	<.001	Not significant
	Study 2	3h	5h	5h	11h	<.001	<.002
Sustained Report of Normal Function (median time)	Study 1	5h	7h	11h	16h	<.001	Not Significant
	Study 2	4h	8h	9h	14h	<.001	.001
Results from Brandes, et al.[8]							
Headache Relief within 2 Hours (% of patients)	Study 1	65	55	44	28	<.001	.009
	Study 2	57	50	47	29	<.001	.03
24-hour Sustained Pain Relief (% of patients)	Study 1	25	16	10	8	<.001	.009
	Study 2	23	14	10	7	<.001	<.001

Against placebo, the combination pill was more effective in relieving headache within the first 2 hours of use. In Study 1 of Brandes, et al., headache relief was reported two hours after receiving doses by 65% of sumatriptan/naproxen users, 55% of sumatriptan users, 44% of naproxen users, and 28% of placebo patients. In Study 2 of Brandes et. al, the differences were 57%, 50%, 47%, and 29% respectively. Differences between each treatment group versus placebo were found to be significant ($p<0.001$ in both Study 1 and 2). A significant difference in the number of patients that were pain free after 2 hours was also found between users of combination therapy and sumatripan alone (Study 1: 65% vs. 55%, $p=0.009$; Study 2: 57% vs. 50%, $p=0.03$).[8]

Brandes, et al. also compared sumatriptan/naproxen versus monotherapy and placebo in providing a sustained 24 hour pain free response. Compared with placebo in both studies, sumatriptan/naproxen was able to provide significant sustained headache relief, pain free response, and relief from nausea, photophobia and phonophobia ($p<0.001$ for all comparisons). The combination pill was also more effective in providing a pain free 24 hour period following treatment compared with sumatriptan alone ($p=0.009$ for Study 1, $p<0.001$ for Study 2).[8]

Landy, et al. utilized data collected on patient questionnaires and diary cards from the above studies to compare ability to function and productivity.[3]

Landy and colleagues used ability to perform work or usual activities as a marker for function. They used a four point categorical scale that included not impaired, mildly impaired, severely impaired, and required bed rest. Diary cards were used to measure pain, function and symptoms. Assessments were completed every 30 minutes for the first 2 hours, and hourly until 24 hours after taking the dose on the diary cards. At baseline, at least 40% of patients in both trials were found to be in either the functional group that was severely impaired or required bed rest.[3]

They found that patients using sumatriptan and naproxen in combination returned to work faster compared to placebo, and were more satisfied with the combination treatment than with other therapies.[3] In Study 1 of Landy et. al, the median time to first reported return to normal function was 4 hours with sumatriptan and naproxen, compared with 4 hours in the sumatriptan group, 7 hours in the naproxen group, and 11 hours in placebo group ($p<0.001$ for both naproxen and placebo groups). In Study 2 of Landy et. al, return to function was significantly better for combination sumatriptan/naproxen than versus either monotherapy or placebo. The median time to first reported return to normal function was 3 hours in the sumatriptan/naproxen group. Both sumatriptan and naproxen alone had a 5 hour median return to normal function ($p<0.002$, $p<0.001$, respectively), while the placebo arm had a median time of 11 hours ($p<0.001$).[3]

Landy, et al. also compared the median time it took to obtain a sustained period of relief after dosing. In both of the Landy et. al studies, use of sumatriptan and naproxen in combination afforded an earlier time to a sustained pain free period, but significance versus sumatriptan alone was only shown in study 2 (4 hours vs. 8 hours, $p<0.001$).[3]

WARNINGS AND ADVERSE EVENTS

Adverse events reported in clinical trials by more than 2% of participants included nervous system, gastrointestinal disorders, pain and other pressure sensations (see table 2). Adverse events reported by more than 1% of patients included flushing, asthenia, palpitations, and muscle tightness.[10]

Sumatriptan is known to cause coronary vasospasms. Sumatriptan-containing therapies, including sumatriptan and naproxen in combination, should be avoided in patients with CAD. In patients with risk factors for CAD, but have otherwise completed a cardiovascular evaluation and are in need of sumatriptan/naproxen therapy, the first dose should be administered while the patient is in a physician's care unless the patient has previously used sumatriptan. Use of sumatriptan-containing products may lead to an increased risk of myocardial ischemia and/or infarction. Sumatriptan and other 5-HT_{1A} agonists can be associated with serious cardiac events and fatalities. NSAIDs, both selective and nonselective, have been associated with an increased risk for cardiovascular thrombotic events.

Patients taking sumatriptan have reported cerebrovascular events including stroke, cerebral and subarachnoid hemorrhaging. It is not clear whether these events were primary and incorrectly perceived as migraine, or what role sumatriptan had in these events. Serotonin Syndrome may occur in patients using 5-HT_{1A} agonists, especially when combined with selective serotonin reuptake inhibitors (SSRIs)

Table 2: Warnings and Adverse Events Associated with Sumatriptan/Naproxen[10]

Adverse Event (reported by > 2% of patients)	Percent Reporting	
	Sumatriptan/Naproxen	Placebo
Dizziness	4*	2
Somnolence	3*	2
Nausea	3	<1
Chest Discomfort/Pain	3*	1
Neck/Throat/Jaw Pain/Pressure/Tightness	3	1
Paresthesia	2	<1
Dyspepsia	2	1
Dry Mouth	2	<1

* Occurred more frequently in sumatriptan/naproxen group than in any monotherapy or placebo groups.

or serotonin norepinephrine reuptake inhibitors (SNRIs).

Both sumatriptan and naproxen can cause significant increases in blood pressure. The combination of sumatriptan and naproxen is contraindicated for patients with uncontrolled hypertension, and should be used cautiously in patients with controlled hypertension. Sumatriptan may cause increases in blood pressure, which could lead to hypertensive crisis, and peripheral vascular resistance. Blood pressure monitoring should be performed during sumatriptan/naproxen therapy.

Because sumatriptan/naproxen contains naproxen sodium, warnings include those commonly seen for NSAIDs. NSAIDs are associated with an increased risk of congestive heart failure and edema. Sumatriptan/naproxen contains naproxen as the sodium salt, and should be used cautiously in patients restricting their sodium intake. Sumatriptan/naproxen should be used cautiously in patients who are retaining fluid or who have heart failure. NSAIDs also carry a risk of GI bleed, perforation, and ulceration.

DOSE

Treximet® is only available in the fixed dose of 119mg sumatriptan succinate, which is equivalent to 85mg of sumatriptan, and 500mg of naproxen sodium.[10] One tablet should be taken at the onset of migraine, with not more than 2 tablets taken in a 24 hour time period.[10] Treximet® may be taken with or without food, though food may delay time to maximum concentration by 0.6 h.[10] Treximet® is not recommended for renally impaired patients (CrCl <30mL/min) and hepatic impairment is a contraindication to therapy due to the fixed dosage of sumatriptan.[10] There are no warnings for use in the elderly.

COST

The average retail price of 3 pharmacies in Gainesville, FL for one bottle of Treximet® is $212.89 (Range $199.98 - $233.70). One bottle contains 9 pills.

SUMMARY

Treximet® is the first combination triptan/NSAID product indicated for acute migraine relief. It is composed of 119mg of sumatriptan succinate (equivalent to 85mg sumatriptan) and 500 mg of naproxen sodium. Treximet® was approved by the FDA in April of 2008. Clinical trials have shown that it is more effective than placebo in relieving migraine 2 hours after use, and is more effective in providing a 24 hour pain free period versus sumatriptan alone, naproxen alone, or placebo.

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RESISTANT URINARY TRACT INFECTIONS

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The Infectious Disease Society of America (IDSA) 1999 guidelines recommend that when trimethoprim-sulfamethoxazole (TMP-SMX) resistant *E. coli* exceeds 10-20% of the total isolates in a community, empirical treatment of urinary tract infections (UTIs) should utilize an alternative agent.[1] Remaining options for empirical treatment include fluoroquinolones (FQs), nitrofurantoin, and fosfomycin. Beta-lactams are not as effective as the aforementioned agents, because common uropathogens have a high level of resistance.[1] Of all of these agents, the FQs are the most effective.[1,2] In the past, FQs were not first-line therapy due to higher cost, worries that resistance might develop, and collateral damage. Recent cost-analyses have shown that FQs become cost-effective when local resistance to TMP-SMX is 19-22%.[3] Also, nation-wide, ciprofloxacin resistance among *E. coli* has remained low, at less than 3%.[4]

On a regional level, certain states in the United States have TMP-SMX resistance that exceeds 20% (see Figure 1).[4] It is in these states especially, but also in those with resistance > 10%, that alternative empiric drug therapy should be considered.[1]

Data from 2001 showed nation-wide average resistance to TMP-SMX to be 16.1%.[4] At the same time, ciprofloxacin resistance was 2.5% and nitrofurantoin resistance was 0.7%.[4] These resistance levels have remained relatively consistent over time (see Figure 2).

Figure 1: Prevalence of TMP-SMX Resistant *E. coli* Throughout the United States. Shaded states have resistance >20%. Most states have resistance >10%, excluding PA, AL, and MO. Data is missing from AK, ME, MT, NV, NM, RI, and WY. Adapted from Karlowsky JA, et al, International Journal of Antimicrobial Agents, 2001.[5]

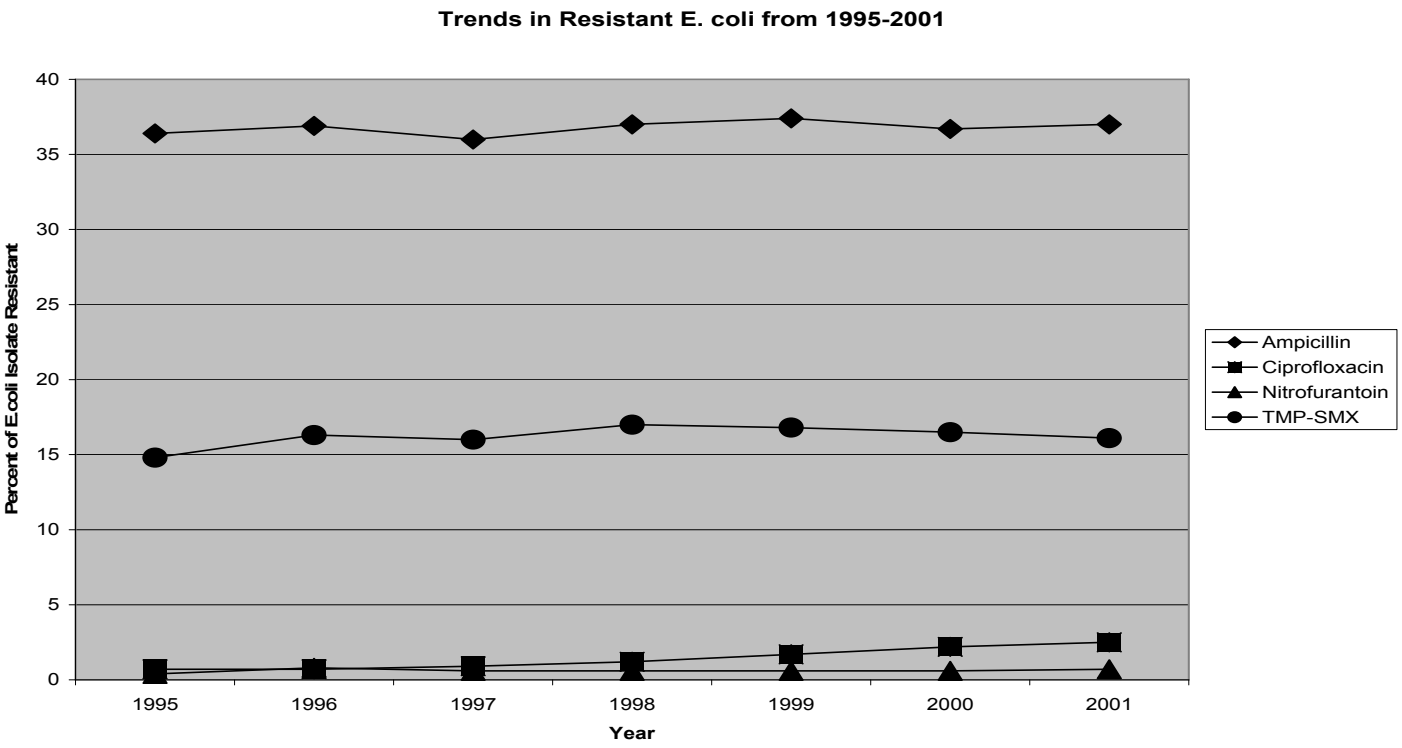

Figure 2: National Percent of *E. coli* Isolates Resistant. Adapted from susceptibility data from the Surveillance Network Database-USA, published in Karlowsky JA, et al, Antimicrobial Agents and Chemotherapy, 2002.[4]

Of the FQs available in the U.S., ciprofloxacin, levofloxacin, gatifloxacin, and norfloxacin have been the most commonly studied. With the development of Cipro XR®, all of these drugs can now be given once a day, except norfloxacin, which requires twice daily dosing.[6] All FQs have similar efficacy in the treatment of UTIs (see Table 1) and treatment choice should depend on cost and ease of dosing.

For uncomplicated UTIs, longer-term regimens are preferred over single-dose treatment (SDT), due to increased bacterial eradication and decreased recurrence (see Table 2).[1]

Other options for UTI treatment include nitrofurantoin and fosfomycin. A head-to-head trial of 521 patients evaluated nitrofurantoin 100 mg BID for 7 days versus fosfomycin as a single 3 g oral dose and found no difference in overall clinical success rate at 32 days ($p = 0.16$; CI -11.1 – 1.3).[14] Several other studies have found similar results, although one study found a significantly increased incidence of adverse events in the fosfomycin arm of the study (fosfomycin 33%, nitrofurantoin 12%).[15,16] These side effects were mostly gastrointestinal or CNS.[16] On the other hand, nitrofurantoin is contraindicated in renal failure and also can cause significant pulmonary and hepatic toxicity when given in high doses or for long durations.[17] Both can be used in pregnancy, an advantage over the FQs which are pregnancy category C.

In comparison to other classes of antibiotics, a small meta-analysis found no difference in adverse effects, eradication, or recurrence between single dose fosfomycin and norfloxacin 400 mg BID for 5-7 days, whereas nitrofurantoin is associated with lower cure rates when compared to TMP-SMX or ciprofloxacin.[1,2,17] More studies need to be conducted on both medications to determine their place in the empiric treatment of UTI. Both will no doubt be increasingly considered as TMP-SMX resistant *E. coli* increases.

Unfortunately, no guidelines for the treatment of UTI have been developed since the IDSA guidelines in 1999. For now, clinical trials and local resistance data drive our empiric treatment of uncomplicated UTI.

Table 1: Review of Fluoroquinolone Head-to-Head Trials

Study	Patient Diagnosis	Study Drugs	Eradication Rates	Statistical Analysis
[7]Peterson J, et al., 2008. (n=1093)	Complicated UTI or acute pye-lonephritis	**Ciprofloxacin** 400 mg IV or 500 mg PO BID for 10 days	86.7%	Levofloxacin is non-inferior to ciprofloxacin
		Levofloxacin 750 mg daily PO/IV for 5 days	88.3%	95% CI (-8.8 to 4.1)
[8]Naber KG, et al., 2004. (n=1095)	Uncomplicated UTI	**Ciprofloxacin** 250 mg BID for 3 days	81.5%	Both gatifloxacin dosing regimens were equivalent to ciprofloxacin
		Gatifloxacin 400 mg IV once	80.5%	95% CI (-5.86 to 8.67)
		Gatifloxacin 200 mg daily for 3 days	82.9%	95% CI (-8.45 to 6.40)
[9]Arrendondo-Garcia, et al., 2004. (n=285)	Uncomplicated UTI	**Ciprofloxacin** 250 mg BID for 3 days	91.8%	Norfloxacin and TMP-SMX were non-inferior to ciprofloxacin
		Norfloxacin 400 mg BID for 7 days	86.9%	95% CI (-2.1 to 14.2)
		TMP-SMX 160/800 mg BID for 7 days	85.2%	95% CI (-0.9 to 16.6)
[10]Auquer F, et al., 2002. (n=325)	Uncomplicated UTI	**Ciprofloxacin** 500 mg single dose	91.2%	Both ciprofloxacin and norfloxacin were equally efficacious
		Norfloxacin 400 mg BID for 3 days	91.9%	p = 0.016

Table 2: Fluoroquinolones: SDT versus Longer-term Treatment

Study	Patient Diagnosis	Study Drugs	Outcome
			Cure rate at 5 weeks:
[11]Arav-Boger R. 1994 (n=113)	Uncomplicated UTI	**Norfloxacin** 1200 mg SDT	63%
		Norfloxacin 400 mg BID for 7 days	83% (p = 0.03)
			Cure rate at 4-6 weeks:
[12]Saignur R, Nicolle LE. 1992 (n=182)	Uncomplicated UTI	**Norfloxacin** 800 mg SDT	78%
		Norfloxacin 400 mg BID for 3 days	88% (p = 0.1, NS)

Table 3: Fluoroquinolones: 3-day Treatment Duration versus Longer-Term Treatment

Study	Patient Diagnosis	Study Drugs	Outcome*		Adverse Effects
[13]Vogel T, et al., 2004 (n=182)	Uncomplicated UTI	**Ciprofloxacin** 250 mg BID for 3 days	Eradication Relapse	98% 15%	Drowsiness ($p < 0.001$), loss of appetite ($p = 0.003$), and abdominal pain ($p = 0.001$) were more common in the 7 day group.
		Ciprofloxacin 250 mg BID for 7 days	Eradication Relapse	93% 13%	

* $p = 0.16$ for the comparison

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