



REVIEW ON: MIGRAINE AND ITS TREATMENT BY TRANSDERMAL PATCHES

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Abstract:

Transdermal patches deliver the drug through the skin in a controlled and predetermined manner in order to increase the therapeutic efficacy of drug and reduces side effect of drug. Triptan that has a favorable tolerability profile and patients have reported greater satisfaction are used in form of patches. It delivers the drug through skin portal to systemic circulation at a predetermined rate over a prolonged period with a fixed amount of dose. Use of the methods outlined in this review in choosing a triptan for an individual patient is probably more likely to get to migraine relief than making an educated guess as to which triptan is most appropriate. There are two non-oral delivery systems nowadays available in the United States for the mild treatment of migraine: three nasal sprays and two injectable formulations. Even though nasal sprays depend partially on nasal mucosal absorption, a significant amount of drug is consumed, transits the stomach and is absorbed in the small intestine, which is not as fast or effective a route of delivery for those migraineurs with gastric stasis.

Keywords: Transdermal patches, skin, triptans, migraine, headache, irritation.

Introduction:

Migraine is a primary headache ailment characterized via way of means of disabling, painful headache assaults related to photophobia, phonophobia, nausea, vomiting and different autonomic signs. The number one headache issues are the maximum common motive for neurological referrals. Migraine is greater not unusual place in girls, with a 1-12 months occurrence fee of 18.2% in girls and 6. five% in men, making it a giant fitness and monetary burden within side the US and worldwide. An extra five.1% of girls and 3.9% of fellows revel in possibly migraine, that is a migraine subtype that fulfils all however one of the International

Classification of Headache Disorders, 2nd edition (ICHD-2) standards for migraine without or with aura of secrecy. The monetary burden of migraine has accelerated significantly within the closing decade, accomplishing an all-time excessive of \$US11.1 billion in direct prices and \$US12 billion in oblique prices in 2002-2004. Currently, the weight likely approaches \$30 billion consistent with 12 months within the US, however no new calculation has been published.⁽¹⁾ Migraine is characterized via way of means of episodes of head ache this is regularly throbbing and regularly unilateral and can be intense. In migraine without aura of secrecy (formerly called not unusual place migraine), assaults are commonly related to nausea, vomiting, or sensitivity to light, sound, or movement. When untreated, those assaults normally closing four to seventy-two hours.⁶ A mixture of capabilities is needed for the analysis, however now no longer all capabilities are found in each assault or in each patient.⁽²⁾ The monetary burden related to migraine is primarily based totally at the incapacitating nature of those episodic assaults. One of the predominant variations among migraine assaults and tension-kind headache or different number one headache issues is their affiliation with intense incapacity regularly attributed to ache or the accompanying nausea and vomiting in addition to different signs. At one time or another, 90% of migraines revel in nausea for the duration of an assault with about 57% of migraines reporting nausea with maximum assaults. Recently, Lipton and associates stated that 73% of migraines revel in nausea and 29% revel in vomiting. The incapacitating nature of migraine is in addition evidenced via way of means of the document that migraineurs withinside the US spend 112 million days bedridden annually. The occurrence of nausea and vomiting is correlated to headache intensity, despite the fact that the precise mechanisms concerned withinside the courting among ache and nausea withinside the migraineurs aren't nicely understood.⁽¹⁾ These signs distinguish migraine from tension-kind headache, the maximum not unusual place shape of number one headache, that is characterized via way of means of the dearth of related capabilities. Any intense and recurrent headache is maximum probably to be a shape of migraine and to be conscious of antimigraine therapy. In 15 percentage of sufferers, migraine assaults are commonly preceded or followed via way of means of brief focal neurologic signs, that are commonly visual; such sufferers have migraine with aura of secrecy (formerly called traditional migraine). In a latest large, population-primarily based totally study, sixty-four percentage of sufferers with migraine had simplest migraine without aura of secrecy, 18 percentage had simplest migraine with aura of secrecy, and thirteen percentage had each sort of migraine (the closing five percentage had aura of secrecy without headache). Thus, as much as 31 percentage of sufferers with migraine have aura of secrecy on a few occasions, however clinicians who rely upon the presence of aura of secrecy for the analysis of migraine will leave out many cases.⁽²⁾ The pharmacological remedy of migraine is a critical a part of the overall routine of accurate control standards for migraine. Pharmacotherapy is historically divided into acute-care and preventive medications. Acute-care remedy (additionally known as abortive remedy) is supposed to opposite assaults after they begin, the purpose being to lessen and preferably prevent the ache, related signs and incapacity. The majority of sufferers simplest use acute-care remedies and get pretty fast relief.⁽³⁾ The migraine-precise 'triptans' have revolutionized the remedy of migraine⁽⁴⁾ and are commonly the gross. Their mechanism of motion is primarily based totally at the stimulation of precise serotonin receptors which includes peripheral five-HT_{1B} and vital and peripheral five-HT_{1D} subtypes. professional withinside the area of headache and constitute the⁽⁵⁾ This outcomes withinside the reversal of vasodilation and a lower in neurogenic Inflammation, in addition to the discount of

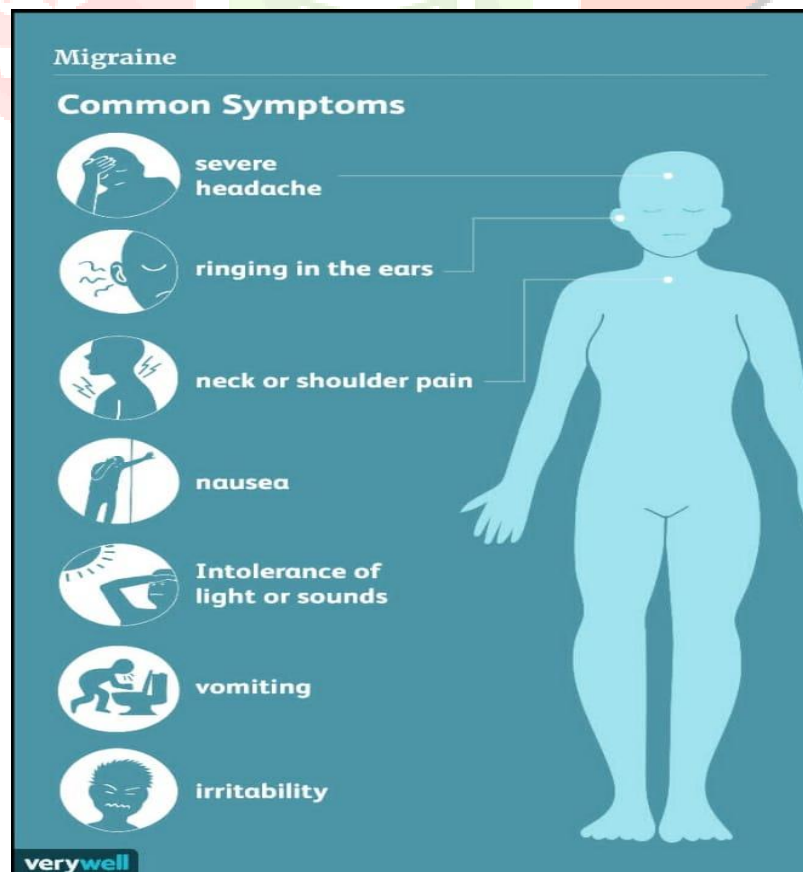
vital nociception. New triptans had been launched in fast succession, with every one demonstrating a few precise pharmacokinetic homes that can be translated into scientific advantages. The purpose of this text is to study the traits of those acute-care migraine-precise capsules and the way their pharmacokinetic attributes cause their use in diverse scientific scenarios.

ASSOCIATED SYMPTOM PREVALENCE:

Migraine ache is always observed with the aid of using different capabilities. Gastrointestinal disturbances are nearly universal, many migraineurs revel in sensory hyperexcitability manifested with the aid of using photophobia, phonophobia, and osmophobia. Other signs and symptoms consist of blurry vision, nasal stuffiness, tenses, stomach cramps, polyuria, pallor, and sweating.

Adults: The related signs and symptoms of migraine make contributions to migraine-associated disability. The maximum distressing related signs and symptoms are gastrointestinal disturbances, considerably nausea and vomiting, which may be intense and incapacitating. Most research file nausea in as much as 90%, vomiting in approximately 50%, and anorexia in maximum sufferers. In addition, meals intolerance, free stools, or actual diarrhea can also additionally arise. Photophobia or phonophobia or each arise in a excessive percentage of migraineurs, and visible disturbances can also additionally arise in as much as 50% of sufferers. In general, the superiority of related signs and symptoms is better in clinic-primarily based totally than population-primarily based totally research, likely due to extra powerful interviewing strategies and extra definitive standards used withinside the clinic. In addition, a choice bias in the direction of sufferers with extra intense headache can also additionally bring about extra signs and symptoms being reported.

Fig 1: Symptoms of Migraine in Adult



Adolescents/Children: The maximum not unusual place signs and symptoms are nausea and vomiting. Nausea seems to arise at decrease prices in kids than in adults, at the same time as the frequency of vomiting seems to be comparable. Nausea and vomiting are extra time-honored in clinic- vs population-primarily based totally research in kids, as in adults. Migraine can be a motive of recurrent episodic vomiting. Many formative years migraineurs have a record of cyclic vomiting, and kids with cyclic vomiting can also additionally increase migraine. Other vegetative signs and symptoms consist of diarrhea, accelerated micturition, sweating, thirst, edema, and shivering. The vegetative signs and symptoms of migraine can also additionally predominate in a few formative years migraineurs. ⁽⁶⁾

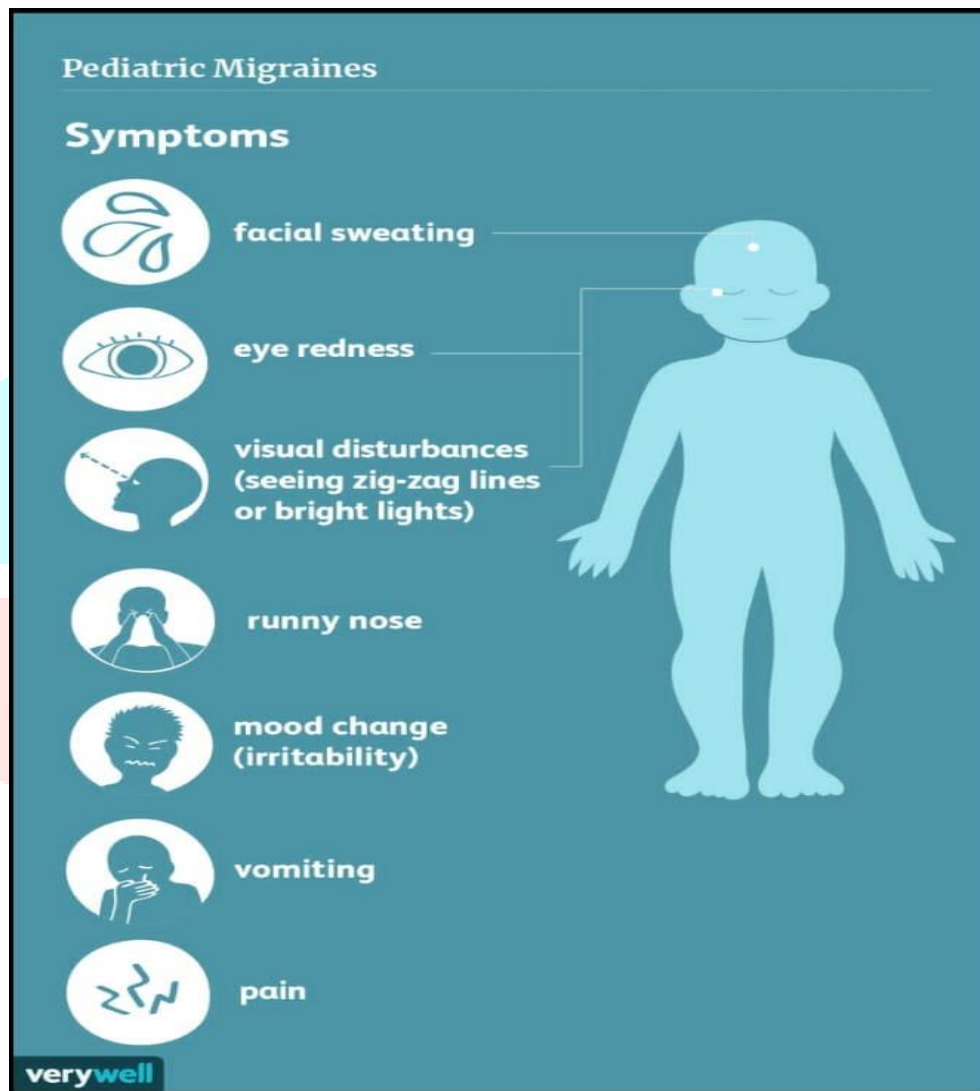


Fig 2: Symptoms of Migraine in Children

PATHOPHYSIOLOGY OF MIGRAINE:

Migraine is pleasant understood as a number one sickness of the mind.⁽⁷⁾ It is a shape of neurovascular headache: a sickness wherein neural occasions bring about the dilation of blood vessels, which, in turn, consequences in ache and similarly nerve activation.⁽⁸⁾ Migraine isn't always due to a number one vascular event. Migraine assaults are episodic and range inside and amongst sufferers. We can also additionally pleasant give an explanation for this variability with the aid of using thinking about the primary biologic hassle in migraine to be the disorder of an ion channel withinside the aminergic mind-stem nuclei that

commonly modulates sensory enter and exerts neural impacts on cranial vessels.⁽⁷⁾ In sufferers with familial hemiplegic migraine, missense mutations within the $\alpha 1$ subunit of the voltage-gated P/Q-kind calcium channel had been identified.⁽⁹⁾ It is viable that different ion-channel mutations make contributions to migraine without air of mystery, considering the fact that it's miles normally instances of migraine with air of mystery which have been connected to the familial-hemiplegic-migraine of using every other gene or genes.

Migraine and the Brain:

As locus.⁽¹⁰⁾ It consequently appears viable that the air of mystery of migraine is become independent from the headache,⁽¹¹⁾ with air of mystery susceptibility genes as its determinant⁽¹²⁾; the ache and related capabilities of migraine itself can be decided with the aid cited above, migraine likely consequences from a disorder of mind-stem or diencephalic nuclei which might be concerned within the sensory — especially nociceptive — modulation of craniovascular afferents. Activation within the mind stem at some point of assaults of migraine has been detected with the usage of positron-emission tomography. Moreover, the air of mystery of migraine is possibly to be the human counterpart of the animal phenomenon of Leão's spreading depression. Aura is characterized with the aid of using a wave of oligemia that passes throughout the cortex on the normally gradual charge of two to six mm according to minute. A quick segment of hyperemia precedes this oligemia and is possibly to be correlate of such signs and symptoms as flashing, jagged lights. Oligemia is a reaction to depressed neuronal feature and remains sincerely gift while the headache starts. These findings, collectively with direct proof that the neighborhood oxygen deliver is extra than adequate, make the belief that migraine is genuinely a vascular headache untenable⁽²⁾

In-Vitro Skin Permeation Studies:

In-vitro pores and skin permeation research could be executed the use of rat's pores and skin. Rat could be sacrificed and pores and skin could be eliminated from stomach portion. Appropriate length of skin could be shaved the use of depilatory cream and this pores and skin could be then used as a barrier among donor and receptor compartment of Franz diffusion molecular. Transdermal patch could be positioned upon it (going through in the direction of stratum carenum of the pores and skin). Receptor compartment could be packed with Phosphate buffer (pH 7.4) and magnetic bead could be positioned within the receptor compartment. Franz diffusion molecular could be positioned upon magnetic stirrer and temperature could be maintained at approximately $37 \pm 0.5^\circ\text{C}$. Samples could be withdrawn at distinctive time c program language period and identical quantity of phosphate buffer could be then brought to the receptor compartment in an effort to hold quantity of the receptor compartment constant. Samples consequently withdrawn could be analyzed through U.V Spectrophotometer in an effort to estimate quantity of drug gift within the sample.

Skin Irritation Studies:

Skin inflammation research could be executed in an effort to hit upon inflammation and sensitization below situations of maximal pressure which might also additionally arise over a extend touch with the pores and skin floor. For this observe rat could be used as an animal model. Patch will be implemented to the shaved pores and skin of the rat on one facet of the returned and secured the use of adhesive tape. On different returned

facet of the rat, manage patch (without drug) could be positioned in a comparable way. Animal could be then stored below remark for a duration of 48hrs to hit upon any signal of erythema, redness, sensitization or some other allergic reaction.

Transdermal patches:

A transdermal patch is a medicated adhesive patch this is positioned at the pores and skin to supply a particular dose of medicine via the pores and skin and into the bloodstream. Often, this promotes restoration to an injured location of the frame. ⁽¹⁴⁾ Its element both passively diffuse from, or are actively transported from, a few parts of the patch. Depending upon the patch, the elements are both brought to the outer floor of the frame or into the frame ⁽¹⁵⁾ Patch presents a managed launch of the drugs into the affected person, generally via both a porous membrane masking a reservoir of medicine or via frame warmth melting skinny layers of medicine embedded withinside the adhesive ⁽¹⁵⁾ This technique of drug transport has the maximum capacity than different routes of management as it avoids issues like gastric inflammation, metabolic variant and because of the presence of meals positive meals-drug interactions might also additionally happen. ⁽¹⁶⁾ A huge type of prescribed drugs are actually to be had in transdermal patch shape which includes migraine condition ⁽¹⁴⁾ Transdermal patches supply the medicament via the pores and skin in a managed and predetermined way in an effort to boom the healing efficacy of drug and decreased facet impact of drug. It offers the drug through pores and skin portal to systemic stream at a predetermined fee over a extended duration with a particular quantity of dose. Success of a transdermal patch relies upon on a whole lot of biological, physiological, biochemical and biophysical factors. It relies upon at the composition, integrity and thickness of the stratum corneum. The shape and length of the molecule are signs of diffusivity. It relies upon at the permeability of the membrane withinside the transdermal drug transport system, nation of pores and skin hydration p and different physiochemical drug properties. ⁽¹⁶⁾ Due to exceptional accessibility, the absence of a primary by skip impact, exceptional blood supply, protection and affected person compliance, patches remedy has emerged as popular. ⁽¹⁷⁾ The patch is fabricated with the aid of using solvent casting technique. The casting solvents and plasticizers used are ethanol and propylene glycol respectively. The polymers used have been HPMC, PVP and EC. ⁽¹⁸⁾ Transdermal patches supply the medicament via the pores and skin in a managed and predetermined way in an effort to boom the healing efficacy of drug and decreased facet impact of drug. It offers the drug through pores and skin portal to systemic stream at a predetermined fee over a extended duration with a particular quantity of dose. Success of a transdermal patch relies upon on a whole lot of biological, physiological, biochemical and biophysical factors. It relies upon at the composition, integrity and thickness of the stratum corneum. The shape and length of the molecule are signs of diffusivity. It relies upon at the permeability of the membrane withinside the transdermal drug transport system, nation of pores and skin hydration pH and different physiochemical drug properties. ⁽¹⁷⁾ It has positive boundaries like sluggish penetration rates, loss of dosage flexibility and use of low dosage tablets are restricted. Its foremost gain is that it avoids first-by skip metabolism. ⁽¹⁶⁾

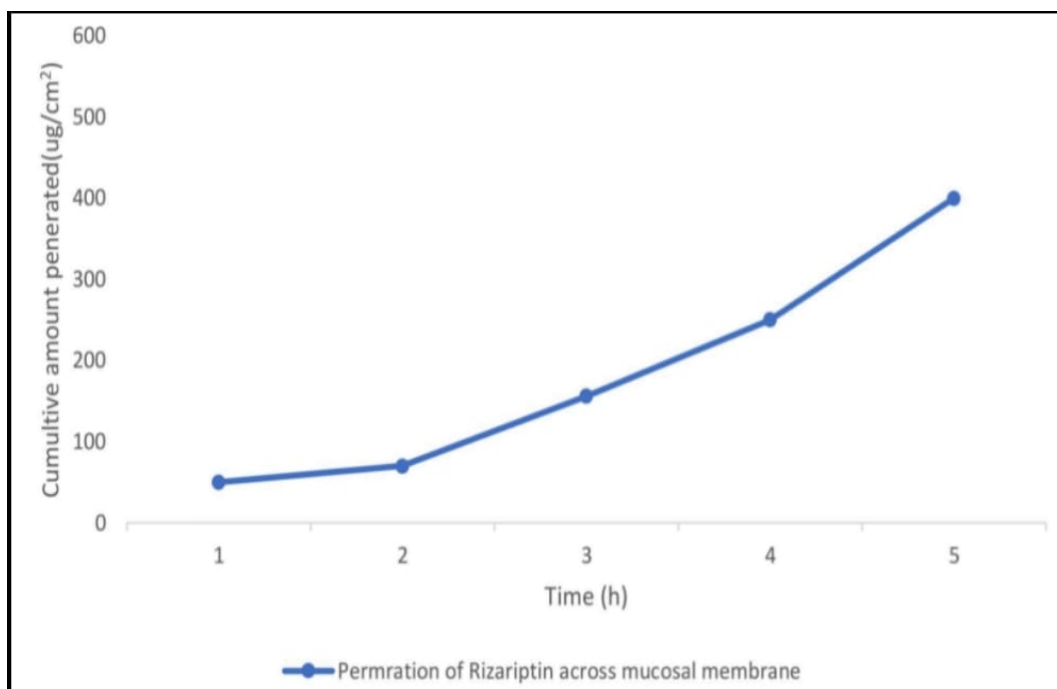


Fig 3: of drug penetration (ug/cm-) through mucosal membrane per hour (h).

Triptans:

These tablets paintings like a mind chemical known as serotonin. It enables pretty down overactive ache nerves. In different words, triptans opposite the modifications your mind that induced your migraine ⁽¹⁹⁾ Triptans like sumatriptan, rizatriptan at the moment are used via patches dosage paperwork to deal with migraine ⁽²⁰⁾ Their mechanisms of motion mediated via the activation of five-HTIB consist of cranial vasoconstriction, the inhibition of calcitonin gene-associated peptide launches and antinociceptive modulation ⁽¹⁷⁾

e.g. Sumatriptan, Rizatriptan, Eletriptans, etc.

Sumatriptan:

Sumatriptan added in an electric powered patch shape implemented to the pores and skin become accepted with the aid of using the Federal Drug Administration (FDA) in 2013 for the extreme remedy of migraine. Sumatriptan become the primary drug in the medicine elegance of triptans to be accepted for the remedy of migraine. It is especially desirable to the ones migraineurs who've ongoing nausea accompanying their complications, the ones for whom a tablet will now no longer paintings, and people with a want for a non-oral medicinal drug to pass the gut. The sumatriptan patch includes a single-use patch that is available in a foil packet. After tabs are pulled to show a small properly of sumatriptan some other properly of salt solution, those regions are every rubbed to launch the 2 compounds. The patch is positioned at the higher arm or thigh, in a place wherein there aren't any tattoos or pores and skin irritation. A tiny battery embedded withinside the patch is then grew to become on with the aid of using pushing a button. A crimson mild comes on, indicating the patch is activated ⁽²¹⁾.

The patch should be grown to become on inside 15 mins of setting it together. The patch stays functioning and in location for four hours.



Fig 4: Marketed formulation of sumatriptan patch

A microprocessor adjusts to the pores and skin, permitting non-stop transport of sumatriptan in a managed dose. A very moderate electric cutting-edge drives sumatriptan via the pores and skin's floor continuously, handing over a complete dose of 6. five mg. This electric powered patch is called an "iontophoretic patch." Up to 2 patches can be utilized in 1 day. ⁽²¹⁾

Mechanism of motion:

Sumatriptan binds with excessive affinity to human cloned five-HTIB/1D receptors. Sumatriptan possibly exerts its healing outcomes withinside the remedy of migraine headache with the aid of using binding to five-HTIB/1D receptors placed on intracranial blood vessels and sensory nerves of the trigeminal system.

The theories proposed to give an explanation for the etiology of migraine headache endorse that signs and symptoms are because of neighborhood cranial vasodilatation and/or to the discharge of sensory neuropeptides via nerve endings withinside the trigeminal system.

The healing hobby of sumatriptan for the remedy of migraine complications is notion to be because of the agonist outcomes on the five-HTIB/1DD receptors on intracranial blood vessels and sensory nerves of the trigeminal system, which bring about cranial vessel constriction and inhibition of pro-inflammatory neuropeptide launch. ⁽²²⁾

Pharmacodynamics:

Blood Pressure: Significant elevation in blood pressure, along with hypertensive crisis, has been suggested in sufferers handled with sumatriptan, with and without a record of hypertension.

Heart Rate: sizable extrude in coronary heart rate.

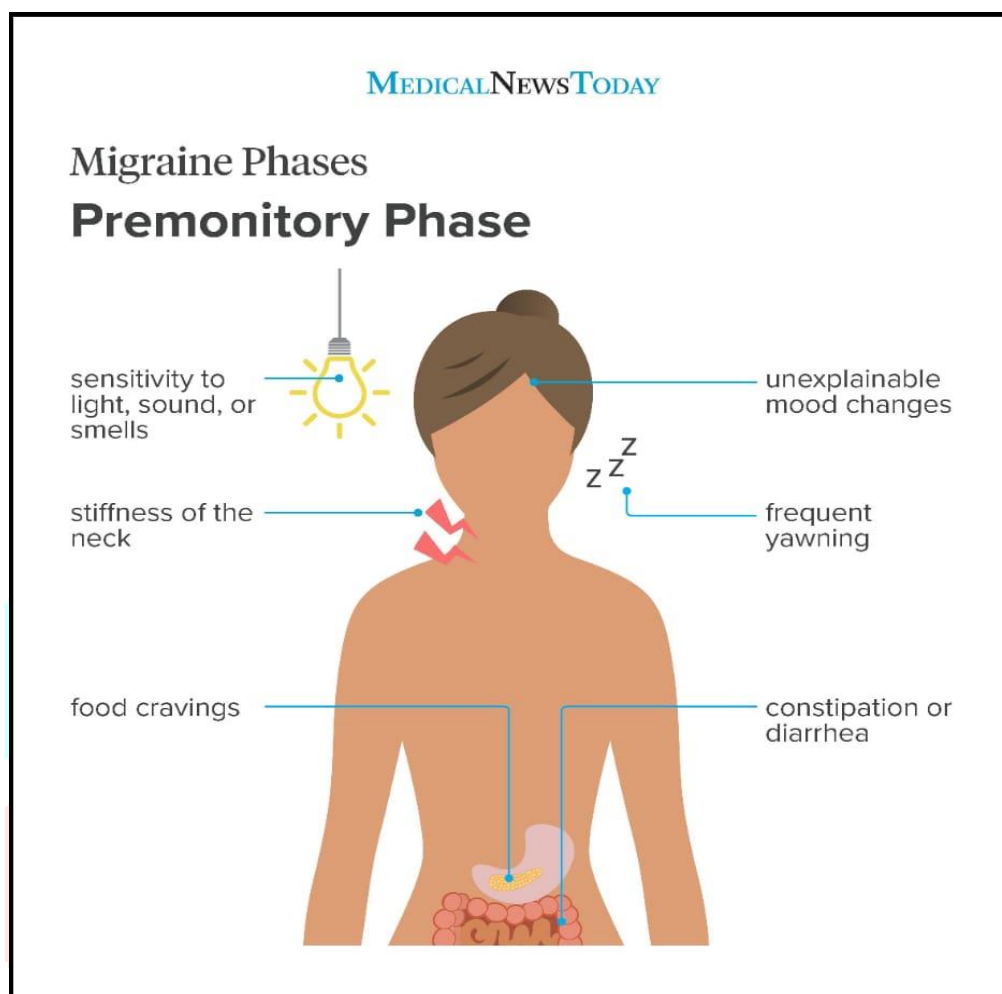


Fig 5: Characteristics of Migraine

Pharmacokinetics:

Half-lives of sumatriptan is 3.1 hr. The obvious the quantity of distribution of sumatriptan is 2. four L/kg. The impact sumatriptan on protein binding of different tablets has now no longer been evaluated ⁽²²⁾. Sumatriptan is metabolized with the aid of using MAO (Mono Amine Oxidase) its metabolites like indole acetic acid (IAA) or IAA glucuronide are excreted via urine. ⁽¹⁶⁾

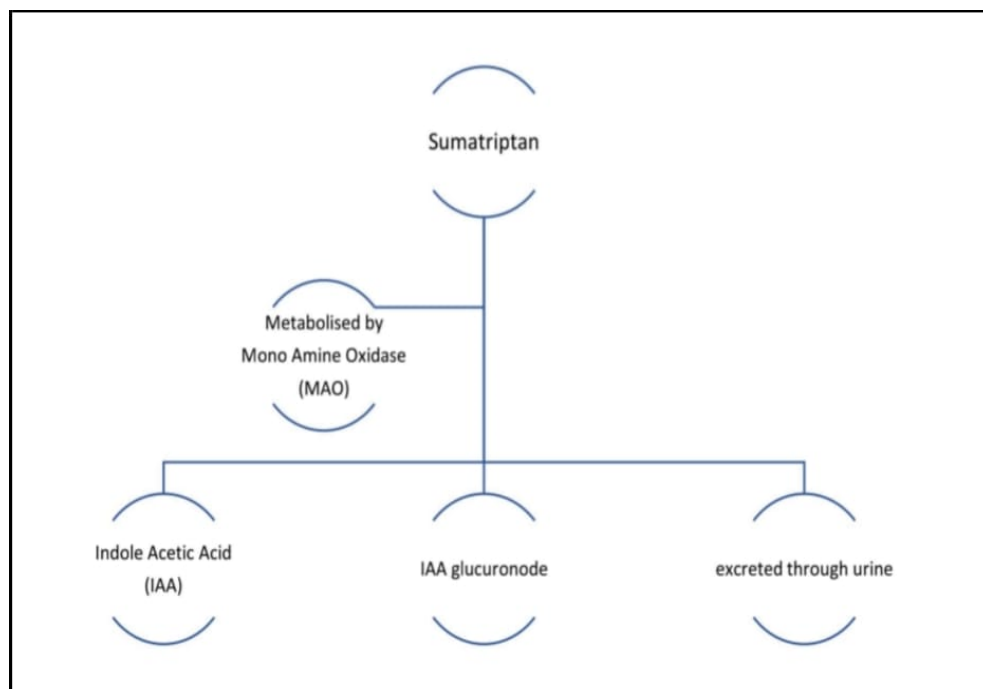


Fig 6: Metabolism of sumatriptan.

Side outcomes:

- Dizziness
- Dry mouth
- Muscle weakness
- Feeling sleepy
- Heavy face, palms and chest
- Allergic touch dermatitis (ACD)
- E.g., Itching, redness, irritations of pores and skin
- Warmth or tenderness of pores and skin
- Raynaud's syndrome
- Peripheral vascular ischemia
- Serotonin syndrome ⁽²³⁾

Precautions:

- It can slim your arteries, when you have threat of :
- High blood pressure
- High cholesterol
- Liver problem
- Diabetes
- Magnetic resonance imaging procedure (MRI): this patch includes steel elements and should be eliminated earlier than an MRI procedure.
- Discontinue remedy if ACD is suspected
- Drug interactions

- Ergot containing tablets: those tablets were stated to motive vasopastic reaction.
- Mono amino oxidase inhibitors
- Other five- HT1 agonist: due to the fact it is able to act through additive impact of vasopastic action.
- Selective serotonin reuptake inhibitors (SSRIS) ⁽²³⁾

Rizatriptan:

Rizatriptan is 2nd technology triptan used as antimigraine agent. It is evolved in patches bureaucracy due it's to low oral bioavailability and significant first by skip metabolism. ⁽²⁴⁾ Transdermal patches supply the drug thru the pores and skin in a managed and predetermined way to be able to growth the healing efficacy of drug ⁽²⁵⁾. Rizatriptan a second technology triptans that has a beneficial tolerability profile and sufferers have stated more satisfaction ⁽²⁴⁾.

Mechanism of action:

Rizatriptan is in a category of medicines referred to as selective serotonin receptor agonists. It works through narrowing blood vessels withinside the brain, preventing ache indicators from being dispatched to the brain, and blockading the discharge of sure herbal materials that motive ache, nausea, and different signs and symptoms of migraine.

Pharmacodynamics:

The plasma drug concentration-time profiles acquired after an unmarried buccal patch management and an oral answer of rizatriptan are illustrated in Figure five. Rizatriptan plasma degree became drastically excessive upon buccal patch. Software in the course of the observe period (as much as 12 h) compared to the oral answer. In each cases, the absorption became rapid, as evidenced through excessive plasma drug degrees detected inside 30 min (buccal, 49.82 + 7.96Ng/mL; oral, 34.32 + 6. seventy-six ng/mL), alaven though statistically enormous ⁽¹⁷⁾.

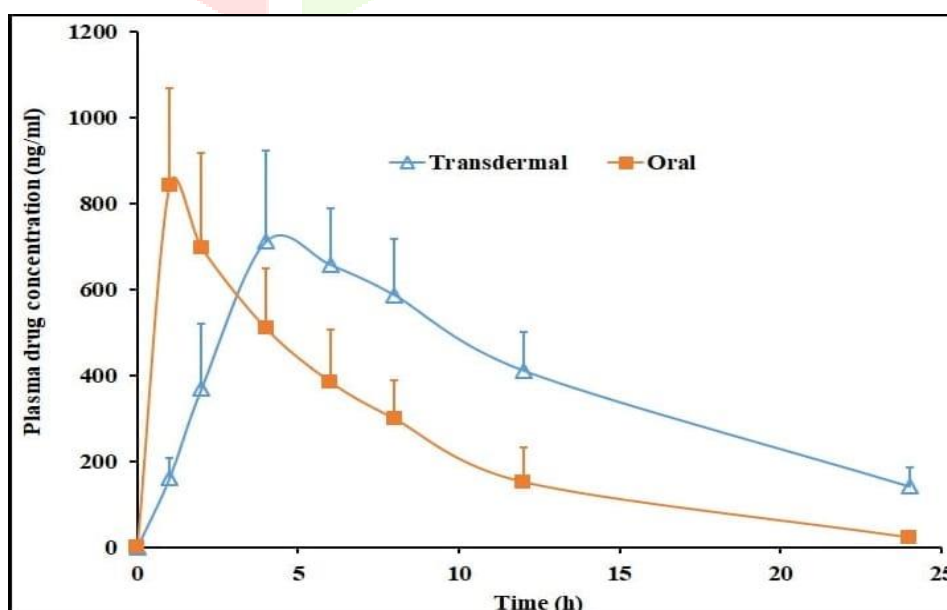


Fig 7: Plasma drug concentration profiles of rizatriptan patch and oral solution.

Pharmacokinetics:

Rizatriptan commonly undergoes significant first pass metabolism within the liver, consequently inflicting a discounted drug plasma degree as in comparison to the buccal patch course. On the opposite hand, the equal T_{max} value (1.5 h) became observed in each the oral and buccal routes.

Buccal patch management exhibited an multiplied C_{max} value (169.43–286.67 ng/mL), which became about two-fold higher ($p < 0.0001$) than its oral counterpart. However, oral remedy of rizatriptan. ⁽¹⁷⁾

Limitations of use:

- Safety and effectiveness of rizatriptan benzoate drugs have now no longer been installed for cluster headache.
- Rizatriptan benzoate drugs need to handiest be used in which a clean analysis of migraine has been installed ⁽¹³⁾.
- Rizatriptan benzoate drugs aren't indicated to be used within the control of hemiplegic or basilar migraine

Contraindications:

- Ischemic coronary artery disease (angina pectoris, records of myocardial infarction, or documented silent ischemia), or different enormous underlying cardiovascular disease.
- History of stroke or temporary ischemic attack.
- Recent use (i.e., inside 24 hours) of any other five-HT₁ agonist, ergotamine-containing remedy, or ergot-kind remedy (inclusive of dihydroergotamine or methysergide) Hypersensitivity to rizatriptan.

Stability Study:

Stability of a drug has been described because the capacity of a specific components, in a particular container, to stay inside its physical, chemical healing and toxicological specification. In a rational layout and assessment of dosage bureaucracy for tablets, balance of the energetic additives should be fundamental standards in figuring out their recognition or rejection. For pharmaceutical dosage form, it's miles important to decide the steadiness take a look at of the dosage form. This will encompass garage at each regular and exaggerated temperature conditions; with the important extrapolations to make certain the product will over its designed shelf life, furnished remedy for absorption on the equal charge as while initially formulated.

ICH specifies the hints for checking out the steadiness of latest tablets products, as a technical required for the registration of pharmaceutical for human use. The ICH hints have installed that long time balance checking out need to be executed at 25 °C at 60 % RH and strain checking out need to be executed at 40 °C/75 % RH for six month ⁽¹⁶⁾. If vast adjustments arise at those strain condition, then the components need to be examined at an intermediate condition (30 °C/ 75% RH). They had been then subjected to in addition assessment research and checked for any parameters.

Therapeutic Objectives:

A precis of the healing goals and cause for the selection of the transdermal course for the energetic substance, in phrases of affected person benefit/ threat, need to be furnished. Factors to be taken into consideration need to encompass healing use, neighborhood and systemic aspect outcomes related to different routes, pharmacodynamics, pharmacokinetic houses of the energetic substance (e.g., $t_{1/2}$, healing index, first by skip-impact). Local tolerance, the approach of management (consisting of occlusion, if applicable), management site, posology, affected person compliance in remedy taking and the proportionality of various strengths need to additionally be mentioned. Where appropriate, move references to applicable medical sections of the file need to additionally be given. The success of the healing goals through the layout and feature of the transdermal patch needs to be absolutely mentioned and correlate with the Description and Composition of the Drug Product e.g. The identity and outline of the form of transdermal patch (e.g., reservoir, drug in adhesive) and the way drug launch over the meant time of software is achieved.

Conclusion:

Preliminary pharmacokinetic studies show that iontophoretic transdermal delivery of sumatriptan provides more constant and predictable therapeutic plasma concentrations other than oral and nasal formulations of sumatriptan, with no evidence of classic triptan-related sensations, including neck and chest pain and pressure impacts. This delivery may assume to be the route of choice for patients with symptoms consistent with gastrointestinal dysfunction (nausea, vomiting, gastric stasis) associated with migraine. Rapid, consistent and precise delivery of stable and optimal therapeutic plasma concentrations of sumatriptan through transdermal patch, without exposing patients to very high concentrations, may lead to superior efficacy and a lower incidence of triptan-related adverse events.

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