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A Unit of Department of Pharmacy Practice

DEVAKI AMMA MEMORIAL COLLEGE OF PHARMACY, CHELEMBRA, MALAPPURAM, KERALA

In the remembrance of

Sri. K.V. Sankaranarayanan

(01.01.1948 - 12.07.2013)

Founder, Devaki Amma Memorial Institutions

With His Heavenly Blessings

The Destination for Excellence

ISSUE HIGHLIGHTS

DEPT HIGHLIGHTS

I) Fixed dose combination value of Valsartan and Sacubitril

Therapeutic category: Valsartan- Angiotensin receptor inhibitor and Sacubitril-Neprilysin inhibitor.

Indication: Chronic Heart failure, Class II to IV.

Brand name: Entresto (Film Coated Tablet).

Mechanism of action: Sacubitril is a prodrug metabolized to the active metabolite LBQ657, which inhibits neprilysin, thereby increasing levels of peptides (such as natriuretic peptides). Valsartan is an angiotensin receptor blocker that selectively blocks the AT1 receptor and inhibits angiotensin-II dependent aldosterone release.

Efficacy comparison: Better compared to Amlodipine besylate (24 hrs mean ambulatory systolic BP), Valsartan (systolic and diastolic BP), Olmesartan (central aortic blood pressure and regular systolic and diastolic BP) and Enalapril (CV death, MI, stroke, heart failure hospitalization).

Dose:

- Initial dose (not currently taking ACE inhibitor or angiotensin receptor blocker, or taking low doses): Sacubitril 24 mg/valsartan 26 mg orally twice daily.
- Initial dose (switching from an ACE inhibitor or angiotensin receptor blocker at a standard dosage): Sacubitril 49 mg/valsartan 51 mg orally twice daily.
- Maintenance dose: Double the dose every 2 to 4 weeks to a target dosage of sacubitril 97 mg/valsartan 103 mg twice daily, as tolerated.
- If switching from an ACE inhibitor, allow a 36-hour washout period before initiating sacubitril/valsartan.

Children: Safety and efficacy is not established.

Dosage adjustment:

- Renal impairment, severe (eGFR less than 30 mL/min/1.73m 2): Initial, sacubitril 24 mg/valsartan 26 mg twice daily; double dose every 2 to 4 weeks to target dosage of sacubitril 97 mg/valsartan 103 mg twice daily, as tolerated.
- Renal impairment, mild to moderate (eGFR 30 mL/min/1.73m 2 or greater): No adjustment necessary.
- Hepatic impairment, severe (Child-Pugh class C): Use not recommended.
- Hepatic impairment, moderate (Child-Pugh class B): Initial, sacubitril 24 mg/valsartan 26 mg twice daily; double dose every 2 to 4 weeks to target dosage of sacubitril 97 mg/valsartan 103 mg twice daily, as tolerated.
- Hepatic impairment, mild (Child-Pugh class A): No adjustment necessary.

Contraindication:

- Angioedema to prior ACE inhibitor or angiotensin II receptor blocker therapy.
- Concomitant aliskiren use in diabetic patients.
- Concomitant use of ACE inhibitors; do not administer within 36 hours of each other.
- Hypersensitivity to sacubitril, valsartan, or any component of the product.

Adverse effects: Hypotension (18%), hyperkalemia (12%), decreased hematocrit and haemoglobin, dizziness (6%), increased serum creatinine level, cough (9%), angioedema.

Drug interactions: ACE inhibitors (hypotension, hyperkalemia, acute renal failure, angioedema), Trimethoprim (hyperkalemia).

Pregnancy and lactation risks: Can cause fetal risks and harmful effects in infants when used during breastfeeding. Avoid the drug and choose alternatives.

Patient advice:

- In case of missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.
- Inform your doctor if pregnant or breastfeeding.
- May feel light-headedness, stand or sit slowly if it occurs.

Prepared by,

Rahib P., Fifth Pharm D.

II) A Review on Sublingual Tablets

Sublingual route is a preferable route and is advantageous over the oral drug delivery due to presence of rich blood supply of blood vessels, rapid onset of action, enhanced bioavailability, bypass first pass metabolism, effects of food, amplified patient compliance and easy self medication. Sublingually administered drug is absorbed by passive diffusion, active diffusion or endosytosis.

Commonly available sublingual tablets

Asenaphine, indicated for Schizophrenia/Bipolar disorder

Buprenorphine hydrochloride, indicated for Opiate addiction

Ergoloid mesylates, indicated for Alzheimers disease

Ergotamine tartarate, indicated for Migraine

Fentanyl citrate, indicated for Cancer pain

Isosorbid dinitrate, indicated for Angina attacks

Nitroglycerin, indicated for Angina attacks

Zolpidem tartarate, indicated for Insomnia

Review on the potential drug candidates as per study findings

In a comparative effectiveness study of sublingual captopril, nifedipine, and prazosin, it was reported that **sublingual captopril** could be a better alternative to sublingual nifedipine in treating emergencies occurring due to hypertension due to lesser side effects.

Sublingual administration of verapamil exhibited significantly higher plasma concentration of the drug (Cmax), a faster absorption rate, rapid ventricular rate reduction and greater bioavailability as compared to its oral administration.

Furosemide showed to offer a therapeutic advantage when administered sublingually over the oral route.

Midazolam was found to be more effective in the emergency treatment of acute febrile and afebrile seizures in children when compared to rectal administration of diazepam.

A research study proposed the office-based treatment of opiate addiction using sublingual administration of **buprenorphine** and **naloxone.**

Zolmitriptan exhibited a faster rate of absorption as compared to subcutaneous injection and was found to be

highly efficient for the treatment of migraine and cluster headaches.

In a randomized, double-blind clinical research study, 40mg of sublingually administered **piroxicam** was found to be as effective as a 75 mg intramuscular injection of diclofenac in the emergency treatment of acute renal colic.

A research study proposed sublingual **epinephrine** as an alternative to self-injected epinephrine for the treatment of anaphylaxis.

Sublingually administered **estrogens** have been shown to exhibit faster drug absorption (i.e., shorter Tmax higher Cmax) than orally administered forms.

Prepared by:

Raihana P.T., Pharm. D. Intern

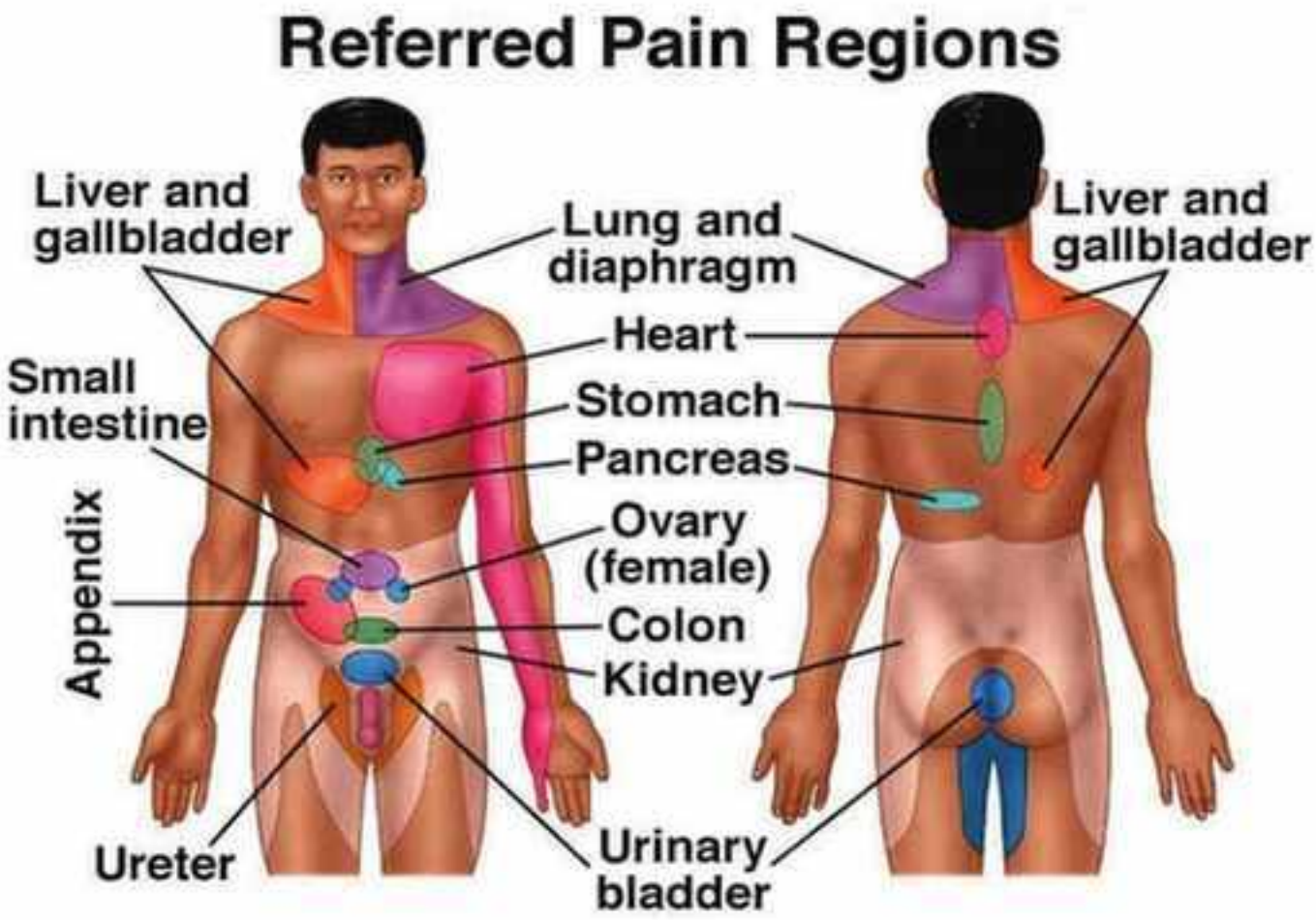
III) Referred Pain

An experience of dental pain during a heart attack is a classical example of referred pain literally stating a pain felt at a site distant from the site of origin. But referred pain can also occur under less dramatic circumstances unrelated to any cardiac pathology. Thus pain referral is frequently found in patients with chronic musculoskeletal pain (for example, temporomandibular disorder (TMD), fibromyalgia, and chronic low back pain). TMD, for example, muscle and/or jaw joint pain could refer to the teeth and other parts of the orofacial area. Pain referral has a neural basis. Specific pathways and neural connections in the brain are thought to lead to the possibility of pain referral. Convergence is one of the important neural phenomena that plays a critical role in pain referral. In concern with the sensory nerves fibres, one group conveys information about touch called touch fibres and another group conveys information about tissue damage or noxious stimulation called nociceptive fibres. Both the nociceptive and the touch nerve fibres convey action potentials into the brainstem to terminate on second order neurones in the trigeminal brainstem sensory nuclear complex. Once in the brainstem, 2 important things can happen. First, many nociceptive sensory fibres from different parts of the orofacial area can terminate on the same set of second order neurones, for example, nociceptive nerve fibres from jaw muscles, tooth pulps, and skin can all converge onto the same second order neuron. Second, both nociceptive and non-nociceptive (e.g. touch, pressure) sensory nerves can converge onto the same second order neurone. The biological reason for this convergence is not totally clear but it appears to be at least part of the reason for referred pain. The second order neurones are part of the pathway that sends sensory information to higher centres for perception. However, since there is so much convergence of sensory information from different body parts onto the same second order neurones, these second order neurones may provide ambiguous information as to the exact location of the noxious stimulus. This neural mechanism is thought to be one way whereby the higher centres of the brain can become "confused" as to the exact location of the noxious stimulus. Another intriguing phenomenon that may help explain pain referral is the unmasking of otherwise silent or latent synaptic connections that may occur with the activation of nociceptive sensory nerve fibres.

Upon entering the brainstem, nociceptive afferent nerve fibres branch extensively to terminate on many different second order neurones that are responsible for conveying information from extensive parts of the orofacial area. Some of these synaptic connections are ineffective or latent and action potentials arriving at these synaptic connections under normal circumstances do not result in activation of the next (second order) neurone in the afferent nerve pathway. It appears that when there is prolonged and/or intense noxious stimulation (for example, muscle trauma or repeated heavy parafunctional clenching), some of these ineffective synapses may become effective connections. Under these circumstances action potentials may be transmitted along pathways that convey information from parts of the orofacial region unrelated to the source of the noxious peripheral stimulus. The brain therefore can become confused as to the correct location of the initiating noxious stimulus. There is a simple diagnostic test that can be done to help distinguish pain referral to a tooth as distinct from pain arising in that tooth.

Clinicians can administer a diagnostic local anaesthetic to produce a neural inactivation at the site where the patient complains of the pain, e.g. a tooth. If the pain being felt in the tooth is referred pain, then the pain should persist despite the local anaesthetic. Such a clinical finding should alert clinicians to the possibility that the pain arises from other sites. Included in the differential diagnosis should be evaluation of muscles and joints for a possible diagnosis of TMD. Treatment of TMDs involves reversible strategies including home-care remedies such as application of moist heat and pharmacotherapy.

Reference: Greg M. Murray. Referred pain. J Appl Oral Sci. 2009 Dec; 17(6): i.



Prepared by:

Raihana P.T., Pharm. D. Intern

IV) A Review on Inhalers

Inhalers are accepted as the most effective way of treating breathing problems compared to tablets and syrups,as the inhaled medication reaches the lungs directly. Inhalers are hand-held, portable devices that deliver medication to your lungs. A variety of asthma inhalers are available. Finding the right one and using it correctly can help you get the medication you need to prevent or treat asthma attacks. Here we are going to review few such inhalers.

Inhaler devices can be classified under 4 categories.

1. Pressurised Metered Dose Inhalers (pMDIs)

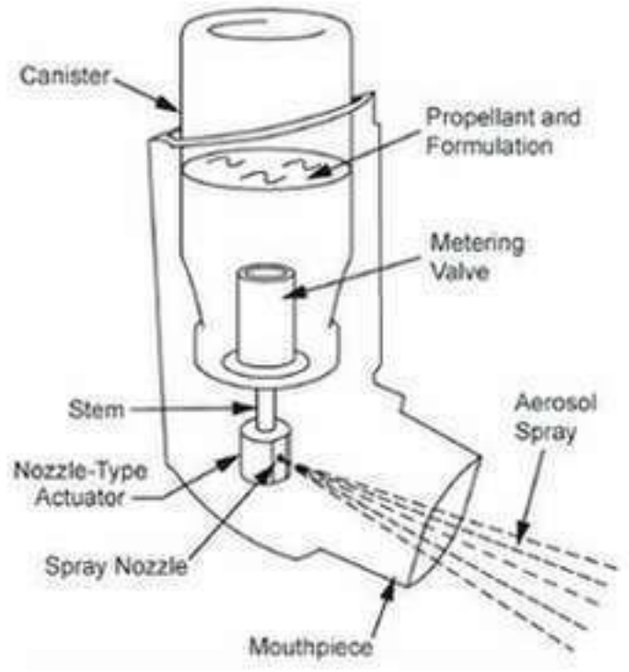
These are the most commonly used inhaler devices. They are propellent-based and deliver a specific amount of medication to the lungs, in the form of aerosol spray; which needs to be inhaled. It releases reproducible doses everytime on actuation.This means that the same amount of dose is released every time.

Additive devices to aid better use of metered dose inhalers include:

a) **Zerostat VT Spacer:** Zerostat VT spacer can be attached to the pMDI. It holds the medication for a little while after the pMDI's actuation. Thus, the spacer helps you inhale all the medication, even if you do not inhale exactly at the same time when the pMDI canister is pressed for releasing the medication.

b) Baby Mask: If a child is unable to hold the Zerostat VT Spacer's mouthpiece properly, you can attach the baby mask to the Zerostat VT Spacer and then use the pMDI. With the help of the baby mask your child can easily inhale

the medicine, while breathing in and out through the mouth normally. It is also useful for those who have difficulty in maintaining a good lip seal on the mouth piece of the pMDI.



Pressurised Metered Dose Inhaler

Spacer

Baby Mask

2. Dry Powder Inhalers (DPIs)

These types of inhalers deliver the medication in a dry powder form. DPIs are breath- actuated devices, which depend on your inhalation, to release the medication from the device. In comparison to the pMDIs, these are easier to use as they don't need propellants. Usually, DPIs are single dose devices, although multi-dose DPIs are available as well. Examples include:

a) Revolizer: The Revolizer is an easy to use DPI, usually used with medication capsules known as rotacaps. It provides an accurate medication dose and a more efficient dispersal, even when the inhalation flow rates are low.

b) Rotahaler: The Rotahaler is an easy to use completely transparent DPI. It is usually used with medication capsules known as rotacaps. Since it is completely transparent, it enables you to make sure that you have inhaled the entire medication.

c) Multihaler: The Multihaler contains preloaded doses in a blister strip, so you do not have to insert a capsule every time you need to take a dose. When you twist (or rotate) the device, it pierces the blister and releases a drug dose. Multihaler also has a dose counter, which enables you to monitor the number of doses remaining in the device.

Revolizer

Rotahaler

Multihaler

3. Breath Actuated Inhalers (BAIs)

An advanced version of the pMDI technology, the breath-actuated inhaler combines the advantages of a pMDI and DPI. The BAI senses your inhalation through an actuator and releases the medication automatically. Example is an Autohaler. The autohaler is by far easier to use than a pMDI and some of the DPIs. It can be used effectively by everyone – children, adults and elderly.

INHALERS DO'S AND DON'T'S

DO'S

- Label your Controller and Reliever inhalers to avoid confusion.
- Breathe out fully before inhaling the medication
- After removing the inhaler from the mouth, hold your breath for about 10 seconds, or as long as it is comfortable.
- If another dose is required, wait for at least 1 minute before taking the second dose.
- Keep a check on the number of doses left in your inhaler.
- In case of dose counters, when the color of the dose counter changes from green to red, indicating fewer doses, consider buying a new inhaler.
- Follow the cleaning and washing instructions mentioned in the patient information leaflet.
- Always keep your inhaler and doctor's prescription while travelling.
- Talk to your doctor and clarify any doubts about the inhalers.

DONT'S

- Do not exhale into your inhaler.
- In case of dose counters, do not tamper with the numbers on the dose counter.
- Do not use the inhaler beyond the expiry date.
- Do not exceed the recommended dose.

Prepared by:

Milka K. Joy, Fifth Pharm D.

Department highlights

I) Publications

1. Siraj Sundaran, Kavya Suresh, Irshad T, Nimmy George, Dona Baiju, G. Babu, Arun Gopalakrishnan and S. Ram Manohar. A study on the prescribing pattern of benzodiazepines in a tertiary care hospital: an observational study. World Journal of Pharmaceutical Research, 2019; 8(9): 438-44.

DEVAKI AMMA MEMORIAL INSTITUTIONS

CHELEMBRA, Near Calicut University, Pulliparamba P.O., Malappuram Dt. Pin -673634, Kerala.
Phone: 0483 - 2891623, 2890695, 2891330

DG DEVAKI AMMA'S GURUVAYURAPPAN COLLEGE OF ARCHITECTURE | DEVAKI AMMA MEMORIAL COLLEGE OF PHARMACY | DEVAKI AMMA MEMORIAL TEACHER EDUCATION COLLEGE | DEVAKI AMMA MEMORIAL TEACHER TRAINING INSTITUTE

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Drug Information Centre,
Department of Pharmacy Practice,
Devaki Amma Memorial College of Pharmacy
Off. Ph: 0495 - 3011333 (Ext-645),
Mob. No: 8281755715
E. Mail: dicdamcop@gmail.com