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TIME MANAGEMENT FOR NEUROLOGISTS

Dr (Prof) Man Mohan Mehndiratta, New Delhi

Time management is essential for a productive and balanced life. Using time management principles helps improve the quality-of-life for an individual by setting priorities and making choices, thus giving the individual a feeling of control and the ability to achieve reasonable goals. Ineffective time management adversely impacts physician career satisfaction. Effective time management requires: Setting short- and long-term goals; setting priorities among competing responsibilities; planning and organizing activities; minimizing exposure to circumstances that result in wasted time. The identification and practice of time management skills will likely improve physician efficiency and career.

MULTIPLE SCLEROSIS-CHANGING TREATMENT PARADIGM WITH NEWER THERAPIES

Dr Bassem I Yamout, Beirut

- Early pathological events in multiple sclerosis (MS) - Axonal transection is irreversible and most abundant in the region of inflammation.
- Early suppression of active inflammation may help to minimize cumulative axonal loss. Early optimized treatment is also essential to prevent progression of MS.
- Exposure to DMDs with a suboptimal effect may lead to development and worsening of disability. Thus, in order to identify patients at risk of poor response and disease progression, it is vital to find out reliable predictors of treatment response.
- Early brain volume loss predicts long-term disability: According to a 10-year retrospective study on the correlation of early whole-brain and central volume loss (n = 261 patients with CIS, RRMS, SPMS or PPMS), rates of both whole-brain and central brain volume loss were significant predictors of 10-year changes in EDSS and MSSS.
- DMTs can be classified under 2 groups: moderate efficacy and high efficacy. Moderate ones can be further categorized as injectables (IFN-beta, peg-IFN-beta-1a, glatiramer acetate) and orals (dimethyle fumarate, teriflunomide, fingolimod, cladribine). On the other hand, high efficacy group can be divided into continuous therapy (natalizumab, ocrelizumab) and noncontinuous therapy (alemtuzumab).
- MS therapy decisions are shared, involving both patient (demographic, lifestyle, emotional and psychological factors, quality-of-life, cognition, fatigue, safety and efficacy, peer perspectives) as well as physicians' (trial data, prognostic factors and disease activity, perceptions of what patients want, cost, logistics and access) perspectives.

A DIALOGUE WITH DR DINESH NAYAK

Dr Dinesh Nayak, HOD and Director of Neurology, Gleneagles Global Health City, Chennai

What is the recommended dosage of lacosamide?

The starting dosage of lacosamide is 100 mg/day and the maintenance dose is between 200-400 mg/day. It is prescribed as a twice-daily dose. Lacosamide can be prescribed as an oral administration and also as intravenous route. For titration, lacosamide can be increased at weekly intervals by 100 mg/day till the maintenance dosage is reached.

What is the pharmacokinetics of lacosamide in epilepsy patients without comorbidities?

Lacosamide has 100% bioavailability with no interactions with food. There is no known effect of food on the absorption of oral lacosamide, therefore, it can be taken with or without food. Lacosamide is less than 15% bound to plasma proteins with an elimination half-life of 13 hours. It takes 3 days to reach the steady-state plasma concentrations.

Are there any known drug interactions and food interactions with lacosamide?

Lacosamide has a low potential for drug-drug interactions. The minimal binding of lacosamide to plasma proteins minimizes the potential for displacement of other drugs. Lacosamide has no interaction or minimal interaction with CYP-450 isoforms, causing minimal effect on the metabolism of other drugs unlikely.

Specific drug-interaction studies involving carbamazepine, valproic acid, omeprazole, metformin, digoxin and an oral contraceptive (ethinyl estradiol and levonorgestrel) also demonstrated no relevant interaction influence on the pharmacokinetics of these drugs or lacosamide.

There is no known effect of food on the absorption of oral lacosamide, therefore, it can be taken with or without food.

How should lacosamide be withdrawn?

As with all antiepileptic drugs (AEDs), lacosamide should be withdrawn gradually (over a minimum of 1 week) to minimize the potential of increased seizure frequency in patients with seizure disorders.

Can lacosamide be used in status epilepticus?

Status epilepticus is among the most common neurologic emergencies, with a mortality rate of up to 20%. The most important therapeutic goal is fast, effective and well-tolerated cessation of status epilepticus. As per Hofler et al, 2013, according to data from studies of refractory status epilepticus treated with lacosamide, the most often used bolus dose was 200-400 mg over 3-5 minutes. The overall success rate was 56%.[1]

What is the effect of lacosamide on depression and anxiety symptoms in patients with focal refractory epilepsy?

Depression is the main psychiatric comorbidity in epilepsy with an estimated prevalence between 20% and 55% and one of the main determinants of quality-of-life. Lacosamide has a positive effect on depressive and anxiety symptoms. The efficacy of lacosamide in seizure control has been demonstrated. However, the antidepressant and anxiolytic effect on mood and anxiety seems to be an independent factor.[2]

References: [1]Höfler J, et al. Epilepsia. 2013;54(3):393-404. [2]Rocamora R, et al. Epilepsy Behav. 2018;79:87-92.

IN CONVERSATION WITH DR VINIT SURI

Dr Vinit Suri; Consultant Neurologist
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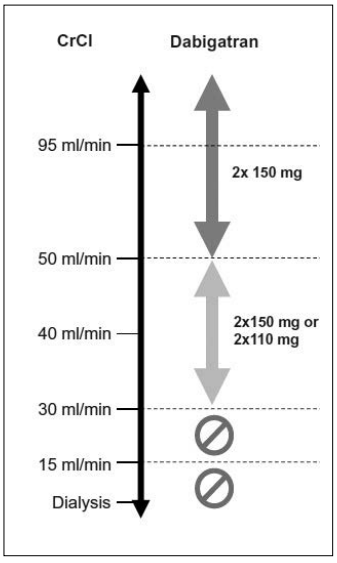
What are the advantages and disadvantages of dabigatran in the indications approved?

Dabigatran is approved for nonvalvular atrial fibrillation, for the treatment of venous thromboembolism and pulmonary embolism and to reduce the risk of recurrent venous thromboembolism and pulmonary embolism. The advantages of use of dabigatran are fixed dosing regimen, no bridging, no INR monitoring and no food interactions and fewer drug interactions. Lastly, it is the only novel oral anticoagulant (NOAC) with an antidote, which makes it 'reversible'. As far as the disadvantages of using dabigatran are concerned, it is difficult to determine the compliance of the patient with the regimen prescribed. Any missed dose may place the patient at increased risk of thromboembolic event and renal monitoring and appropriate dose adjustment is required.



What all should be considered regarding the dosage and variance of use of dabigatran (150/110/75)?

Dabigatran is indicated for nonvalvular atrial fibrillation: *For patients with CrCl >30 mL/min:* 150 mg orally, twice-daily; *For patients with CrCl 15-30 mL/min:* 75 mg orally, twice-daily:

- Patients who are not able to tolerate the dose of 150 mg due to side effects can be given 110 mg; however, the recommended dose is 150 mg
- Do not use if CrCl <15 mL/min
- Avoid in pregnancy, breastfeeding or in severe liver disease.

What are the drug interactions of dabigatran vs. warfarin?

Treatment with vitamin K antagonists (VKAs) requires careful consideration of multiple food and drug-drug interactions. Despite fewer interactions with the NOAC drugs, physicians should consider the pharmacokinetic interactions of accompanying drugs and comorbidities when prescribing NOACs.

Can dabigatran be prescribed in patients with renal impairment?

Studies have reported up to 3-fold increase in drug exposure. In moderate renal impairment, the reported major bleeding rate was comparable between dabigatran 110 mg and 150 mg. A reduced dose may be considered in these patients. The presence of one or more factors known to increase hemorrhagic risk may increase the risk of bleeding. Caution should therefore be exercised.

Close clinical surveillance is recommended. Dabigatran etexilate is contraindicated in cases of severe renal impairment (CrCL <30 mL/min). Patients who develop acute renal failure should discontinue dabigatran etexilate.

Should dabigatran be withdrawn in any situations?

Emergency surgery or urgent procedure

Dabigatran etexilate should be temporarily discontinued. The specific reversal agent idarucizumab could be useful for the rapid reversal of the anticoagulation effect.

Elective surgery/intervention

If possible, dabigatran should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete hemostasis may be required, consider stopping dabigatran etexilate 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer.

Dabigatran is contraindicated in patients with severe renal dysfunction (CrCL <30 mL/min) but should this occur then dabigatran etexilate should be stopped at least 5 days before major surgery.

Acute surgery/intervention

An acute surgery/intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed, there may be an increase in the risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Spinal anesthesia/epidural anesthesia/lumbar puncture

Procedures such as spinal anesthesia may require complete hemostatic function. In patients treated with dabigatran etexilate and who undergo spinal or epidural anesthesia, or in whom lumbar puncture is performed in follow-up to surgery, the formation of spinal or epidural hematomas that may result in long-term or permanent paralysis cannot be excluded.

The risk of spinal or epidural hematoma may be increased in cases of traumatic or repeated puncture and by the prolonged postoperative use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms.

How to measure the anticoagulant effect of dabigatran?

For dabigatran, the aPTT may provide a qualitative assessment of dabigatran level and anticoagulant activity. The relationship between dabigatran and the aPTT is curvilinear. Dabigatran has little effect on the PT and INR at clinically relevant plasma concentrations, which are therefore unsuitable for the assessment of the anticoagulant activity of dabigatran.

How to deal with dosing errors?

To avoid dosing errors, patients on NOACs should be encouraged to make use of well-labeled weekly containers, with separate spaces for each dose timing. Importantly; however, dabigatran must not be taken out of its original bottle until immediately before intake.

A forgotten dose may be taken until 50% of the dosing interval has passed. Hence, for NOACs with a BID dosing regimen (i.e., every 12 h), a forgotten dose can be taken up until 6 hours after the scheduled intake. For NOACs with an OD dosing regimen, a forgotten dose can be taken up until 12 hours after the scheduled intake. After this time point, the dose should be skipped and the next scheduled dose should be taken.

Source: Steffel J, et al. Eur Heart J. 2018;39(16):1330-93.

ROLE OF ROSUVASTATIN IN PREVENTION OF STROKE

Dr U Meenakshisundaram, Senior Consultant (Neurology), Apollo Hospitals, Chennai

Statins are known to be effective in primary and secondary prevention of stroke. They have long-term beneficial effects that seem to be mediated by their lipid-lowering potential. Statins can also prevent recurrence or progression during acute stage of stroke on account of their antithrombotic, anti-inflammatory and antioxidative effects.[1]

The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial assessed the effect of statins in reducing vascular events in healthy adults with normal cholesterol level <130 mg/dL and elevated sensitive C-reactive protein (s-CRP). The study had to be terminated early when the benefits of the treatment arm were found to be highly significant for the treatment arm in reducing stroke, myocardial infarction (MI) and the need for revascularization. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively, with corresponding rates of 0.18 and 0.34 for stroke, and 0.45 and 0.85 for the combined end point of MI, stroke or death from cardiovascular (CV) causes.[2] The trial provided substantial evidence that starting statin therapy in patients without elevated cholesterol led to a significant reduction in the risk of stroke. In the

JUPITER trial, rosuvastatin reduced the incidence of ischemic stroke by more than half among men and women with low levels of LDL cholesterol who are at risk because of elevated levels of hs-CRP.[3] Therefore, when used in primary prevention among individuals with LDL <130 mg/dL and hs-CRP ≥2 mg/L, rosuvastatin has been shown to significantly reduce first MI, stroke, arterial revascularization, hospitalization for unstable angina and CV death in whites as well as non-whites.[4] In post hoc analyses of the JUPITER trial requested by European health authorities, among primary prevention patients with elevated hs-CRP having high global CV risk (10-year Framingham risk score >20% or SCORE risk ≥5%), but low LDL cholesterol levels, rosuvastatin significantly reduced major CV events. During 1.8-year median follow-up (maximum 5 years) of patients with Framingham risk >20%, the rate of MI/stroke/CV death was 9.4 and 18.2 per 1,000 person-years in rosuvastatin and placebo groups, respectively.[5] In the HOPE-3 trial, significantly fewer subjects in the rosuvastatin group had strokes, as compared to the placebo group. Fewer ischemic strokes occurred in the rosuvastatin group than in the placebo group (41 vs. 77).[6]

Rosuvastatin has also been used successfully in secondary prevention. A meta-analysis revealed that rosuvastatin is better than atorvastatin in the prevention of major CV events when statins are used in the secondary prevention of CV diseases.[7] A randomized, double-blind, multicenter trial compared rosuvastatin 20 mg and placebo in statin-naïve stroke patients. Hemorrhagic infarction or parenchymal/subarachnoid hemorrhage on gradient-recalled echo MRI occurred less frequently in the rosuvastatin group (6/137, 4.4%) as compared to the placebo group (22/152, 14.5%). Additionally, among 314 patients with at least one dose of study medication, progression or clinical recurrence of stroke was less frequent in the rosuvastatin group (1/155, 0.6% vs. 7/159, 4.4%).[1] Another study revealed that rosuvastatin therapy prevented aortic arch plaque progression in ischemic stroke patients with complicated aortic arch plaques (CAP), and seemed to have long-term clinical benefits. Patients with CAP not taking rosuvastatin had significantly more major adverse cerebrovascular events (MACEs) than those with CAP taking rosuvastatin, and those without CAP. Patients with CAP taking rosuvastatin also showed significant improvement in CAP diameter with improved lipid profiles.[8] Large atheromatous aortic plaques (AAPs) are known to be associated with ischemic stroke. It was shown in the EPISTEME trial that treatment with rosuvastatin for 6 months induced AAP stabilization with considerable LDL cholesterol reduction in patients with ischemic stroke.[9]

References: [1]Heo JH, et al. J Stroke. 2016;18(1):87-95. [2]Ridker PM, et al. N Engl J Med. 2008;359(21):2195-207. [3]Everett BM, et al. Circulation. 2010;121(1):143-50. [4]Albert MA, et al. Am Heart J. 2011;162(1):106-14.e2. [5]Koenig W, et al. Eur Heart J. 2011;32(1):75-83. [6]Yusuf S, et al. N Engl J Med. 2016;374:2021-31. [7]Zhong P, et al. Drug Des Devel Ther. 2017;11:2517-26. [8]Kaneko K, et al. Neurol Res. 2017;39(2):133-41. [9]Ueno Y, et al. Atherosclerosis. 2015;239(2):476-82.

CERVICOGENIC HEADACHE: DOES IT EXIST?

Dr Sumit Singh, Gurugram

- Yes, it does exist.
- Cervicogenic headache - Pain confined to, or originating in the cervical region. It may radiate to the other side or the head or the shoulder region.
- Multiple sources of headache may be present within the same patient.
- Convergence of upper cervical segment nociceptive afferents in the trigeminocervical complex - Anatomical basis for both headache and neck pain to frequently co-exist.
- Both Neurologists and Pain Specialists should reconcile these intersections and address the multiple sources of pain in those headache patients who present with both headache and neck pain.
- Team of experts working together is the solution.
- Oversimplification of the diagnosis to migraine alone or cervicogenic headache alone may leave the patient with inadequate treatment.

SECONDARY CAUSES OF PERIPHERAL DEMYELINATION

Dr Tapas Kumar Banerjee, Kolkata

- The causes of secondary demyelinating neuropathy include paraproteinemia related disorders, lymphoma, sarcoidosis, certain infections and drugs.
- IgM paraproteinemia is an important cause of demyelinating polyneuropathy, usually not responsive to conventional treatment.
- Biologic therapy with monoclonal antibodies, namely, rituximab, ocrelizumab, ofatumumab, etc. have been of benefit and have changed the outcome of these previously untreatable diseases.

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