

Imaging in Acute Ischemic Stroke

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Abstract : With recent advances in imaging and efficacious treatment of cerebral ischemia, the role of imaging and neuroradiologist has become central from peripheral. CT scan can be done as an initial imaging of clinically suspected patient of stroke mainly to rule out hemorrhage and stroke mimickers like mass lesion. CT angioplasty and perfusion imaging can be performed to look for major vessel occlusion and tissue at risk. MR imaging is better imaging modality to diagnose acute ischemic stroke with use of diffusion weighted imaging. Perfusion and diffusion mismatch are very much suggestive of salvageable brain parenchyma. MRA and MRS can be further supportive in strengthening the diagnosis of ischemic stroke. DSA and intravenous and intraarterial thrombolysis are established ways of treatment of acute ischemic stroke patients when performed within 6 hours of onset of symptoms (window period).

INTRODUCTION

Stroke is an injury to the central nervous system that is characteristically abrupt in onset and due to a vascular insult. The term is reflective of damage to the brain secondary to ischemia or hemorrhage. It is the number three cause of mortality and the number one cause of disability in adults in the United States. Strokes are ischemic approximately 80% of the time, and until recently, there was no available beneficial intervention¹. In 1995, the published results of the National Institute for Neurological Diseases and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) trial represented the first demonstration of efficacious treatment for acute cerebral ischemia². This has redefined the role of the radiologist and neuroimaging from peripheral to central in the management of acute cerebral ischemia.

COMPUTED TOMOGRAPHY

Computed tomography (CT) is an established basic and most important tool for the diagnosis of ischemic or hemorrhagic stroke. CT imaging protocol for ischemic stroke includes - Non Enhanced Scan, CT perfusion and CT angiography on multislice scanner.

Nonenhanced CT can help exclude hemorrhage and detect "early signs" of infarction but cannot reliably demonstrate irreversibly damaged brain tissue in the hyperacute stage of ischemic stroke.

Dynamic contrast enhanced CT scan or Perfusion CT provides information about brain perfusion, which permits differentiation of irreversibly damaged brain tissue from reversibly impaired "tissue at risk".

CT angiography can help detect stenosis or occlusion of extra and intracranial arteries. Use of these three imaging techniques - nonenhanced CT, perfusion CT and CT angiography - assist in rapidly obtaining comprehensive information regarding the extent of ischemic damage in acute stroke patients.

NONENHANCED COMPUTED TOMOGRAPHY (CT)

Used until the late 1980s primarily to exclude hemorrhage in patients with acute stroke. Requirements for diagnostic imaging in patients with ischemic stroke changed as a result of the 1995 study by the

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National Institute of Neurological Disorders and Stroke (NINDS)². With the interruption of blood flow, the energy needs are no longer met, resulting in cytotoxic edema, which is defined as cellular injury with influx of fluid in the intracellular space without an increase in vascular permeability³.

Neurons, located in gray matter are the most sensitive cell to ischemia. Initially these are more dense than the white matter, later becomes increasingly less dense with an increase in water content.

The CT signs of acute cerebral infarction (Fig.1) :

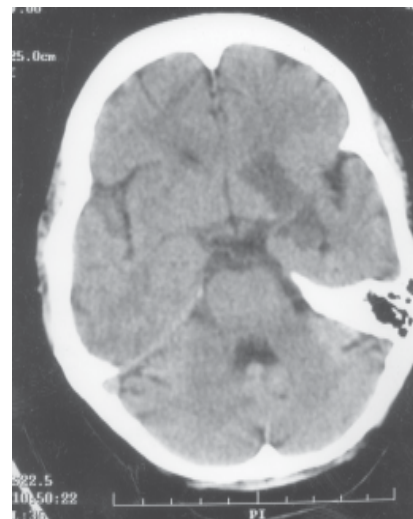


Fig.1 : CT scan brain showing a well defined hypodense wedge shape area of infarct involving head of left caudate nucleus

- (a) blurring of the clarity of the internal capsule,
- (b) loss of distinctness of the insular ribbon cortex,
- (c) loss of differentiation between the cortical gray matter and the subjacent white matter^{4,5} and
- (d) Due to the accumulation of intracellular fluid causing swelling of the Gray matter. This results in effacement of the spaces demarcated by the gyral infoldings (sulci) known as "sulcal effacement"⁶.

The “*hyperdense MCA sign*” is secondary to an embolus lodged in the MCA. This results in increased attenuation in the first segment of the MCA⁷. Angiographic correlation has demonstrated a corresponding thrombus. This sign is associated with worse patient outcomes. A similar “hyperdense” vessel sign has been described for the basilar artery. Whereas prominence of the parenchymal changes associated with vascular occlusion are a contraindication to thrombolysis, the “hyperdense MCA sign” signifies a vascular occlusion and a need for intervention when detected within the treatment window. However false positive hyperdense MCA sign can be seen in polycythemic, vessel calcification, post contrast scans and dehydrated patients and false negative in anemic patients. Administration of contrast material may be helpful in delineating infarcts in the subacute period when there may be obscuration of the infarct by “*fogging*”⁸. Fogging is described as the phenomenon of an area of previously hypoattenuating infarction evolving to a state of isoattenuation between days 14 and 21 after infarction; this occurrence was believed to be secondary to small potechial hemorrhages or infiltration of the infarcted tissue with macrophages⁹. Although difficult to see on a nonenhanced study, the area of infarction intensely enhances at the periphery.

In summary, nonenhanced head CT has a clearly defined role in the current management of acute stroke. A CT scan for the exclusion of hemorrhage. CT is appealing as an imaging study in that it is widely available, can be performed quickly and safely on critically ill patients, and is relatively inexpensive. Further, its utility has been proved in large-scale clinical trials.

Limitation of NCCT in stroke : (1) Up to 60% of CT scans are normal in the first few hours after ischemic insult. (2) Another 10%-20% had arterial dissections, occlusions sites not readily susceptible to thrombolysis, or minor branch occlusions that without intervention have a favorable natural outcome¹⁰. The lack of sensitivity and specificity in the diagnosis of stroke limits the attainable benefit.

CT PERFUSION

Viability of the cerebral parenchyma is dependent on cerebral blood flow (CBF). The assessment of cerebral perfusion in patients with acute stroke, in a clinically relevant time frame, is of utmost importance for patient selection before thrombolytic therapy. Quantitative mapping of CBF to indicate the severity and potential reversibility of neuronal damage can be used to predict which brain tissue will be salvaged with reperfusion or die without it (pneumbra), as well as which brain tissue is already infarcted. Perfusion CT offers a number of practical advantages like it can be performed immediately after unenhanced CT and used in general to exclude cerebral haemorrhage. It is fast (typical procedure time < 5 min) and does not require specialized computer hardware¹¹.

Limitations of CT perfusion : (1) Limited sample volume. Whole brain cannot be studied even with newer 64 slice CT scan. (2) Patient motion causes false registration of perfusion values and hence incorrect results. (3) Beam hardening due to any reason causes interpretation of perfusion study fallacious¹².

CT ANGIOGRAPHY

Computed tomographic (CT) angiography is a new method for evaluating vascular anatomy. Making use of slip-ring technology

and multi slice CT scan, visualization of vascular anatomy after intravenously administered iodinated contrast medium has been recently shown to be reliable alternative to MR angiography in the detection of arterial anatomy in the circle of Willis. It has shown promise in the evaluation of carotid bifurcation disease as well as for intracranial aneurysms and vascular malformations¹³.

MRI

The diagnosis of intracerebral hemorrhage (ICH) is still a domain of CT rather than MRI, especially in acute stroke. The key substrate for MRI visualization of hemorrhage is deoxyhemoglobin, which causes a signal loss in T2-weighted imaging (T2-W1) because of paramagnetic susceptibility effects, although usually not within the first 12 to 24 hours. MRI has proved superior to CT scan in diagnosis of ischemic stroke with recent introduction of new multimodal MRI (mMRI) techniques such as diffusion and perfusion-weighted imaging (DWI and PWI) has improved diagnostic imaging in hyperacute ischemic stroke¹⁴. **Diffusion weighted MRI (DWI)** can render ischemic fields visible within minutes of ischemia onset and extent of ischemia.

Magnetic resonance angiography (MRA) allows rapid characterization of the cervical and cephalic large vessels. MRA detects and grades cervical internal carotid stenosis with an accuracy of 85% to 96% compared with digital subtraction angiography. With the use of MRS, stenosis and occlusions of intracranial vessels are identified with 80% to 100% sensitivity and specificity compared with catheter angiography¹⁵.

Together, DWI and cervical and cephalic MRA have the potential to identify the site of brain ischemia and the site of large vessel disease within the first hours after stroke onset and hospital admission, providing detailed pathophysiological information.

CONVENTIONAL MR IMAGING

Acute infarcts are better and more visible on MR images than on CT scans, with over 80% of MR images positive in the 1st day compared to 60% of CT scans. MR imaging is particularly superior in the detection of stroke in the posterior fossa where CT is limited due to beam-hardening artifact from the adjacent skull base. **Lacunar infarcts** and **small cortical strokes** are also seen with higher conspicuity¹⁶.

The earliest MR changes are loss of normal intravascular flow voids, morphologic swelling of the gray matter and increased signal intensity on the T2 weighted and intermedate-weighted images. There is normally a loss of intraarterial signal with standard spin-echo (SE) sequences, referred to as a “*flow void*” in low-or-no flow states, there is a loss of the “flow void” such that signal intensity is demonstrated in the involved vessel. Similar to the “hyperdense MCA sign” in CT, absence of flow in involved vessels can be seen immediately after occlusion. The earliest signal intensity changes usually involve the gray matter, with the white matter typically appearing normal in the first 24 hours. Intermediate-weighted images enable differentiation of lacunar infarcts from perivascular spaces; the former hyperintense and the latter isointense to CSF¹.

Intravenous contrast material can provide additional information. Vascular enhancement can be seen in cortical infarcts up to 75%

of the time. This is believed to be due to slow flow in the region of the infarction. Meningeal enhancement can also be seen acutely in approximately 33% of patients, possibly due to meningeal inflammation. Both types of enhancement resolve toward the end of the 1st week. Administration of contrast material is now typically reserved for those instances in which MR perfusion imaging is performed¹⁷. A fast SE sequence enables the acquisition of T2-weighted images in a fraction of the time (roughly four to 16 times faster). Modified fast FLAIR and fast SE FLAIR can reduce imaging time to 2-5 minutes. Acute infarct appears as hyperintense on T2 weighted and intermediate (FLAIR or PD) images and iso to hypointense on T1 weighted images (Fig.2).

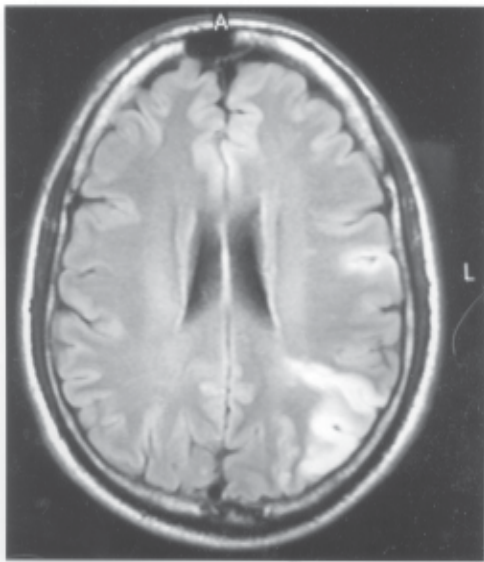


Fig.2 : MRI brain T2 FLAIR image showing areas of hyperintensity involving left parietal and few areas of frontal cortical and sub cortical white matter suggesting acute ischemic infarct

MR DIFFUSION IMAGING

Cytotoxic oedema which is due to accumulation of intracellular water minutes after onset of acute cerebral ischemia, causes restriction (decrease in) of microscopic diffusion of protons. In diffusion weighted MRI, this is reflected as decrease of the apparent diffusion coefficient (ADC). It appears hyperintense on diffusion weighted images (DWI) (Fig.3).

The apparent diffusion coefficient (ADC) decreased by approximately 30-50% within 30 minutes after onset of focal ischemia. This change occurs while other MR image types such as T2 or intermediate weighted images remain normal. It is generally believed that the most likely cause of the decrease in ADC values is the redistribution of water from the interstitial to the (diffusion-restricted) intracellular space, as the energy-dependent Na^+ , K^+ -ATPase pumps fail (i.e. the initiation of cytotoxic edema¹).

MR PERFUSION IMAGING

Perfusion imaging can detect hypoperfused regions of brain either by monitoring the transit of a rapidly injected contrast agent⁶ or

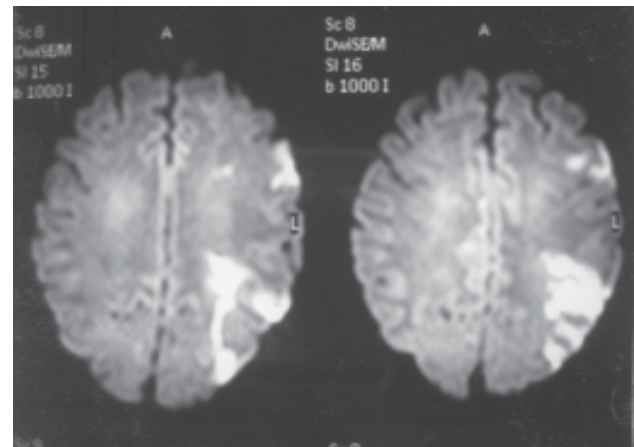


Fig.3 : Diffusion weighted image of same patient in Fig.2 showing hyperintensity on B1001 suggesting restricted diffusion in areas of acute ischemic infarct

magnetically tagged water molecules in arterial blood through the brain⁷. In region distal to arterial occlusion the arrival of contrast may be delayed and less in amount. The resulting signal - time curve can be converted into concentration - time curve, from which several functions like CBV, rCBF, TTP, MTT that describe regional perfusion can be determined and compared from normal side. A variety of perfusion abnormality has been described like reduced rCBF in the region of ischemia.

Varying pattern of "mismatch" between lesion extent on DWI and PI can occur.

- * PI lesion > DWI lesion - larger area of brain is under threat of ischemia than shown by DWI alone.
- * PI lesion = DWI lesion - the brain parenchyma at risk is minimum and final infarct may be of the size shown by either of image.
- * PI lesion < DWI lesion - suggest that reperfusion has occurred in the infarcted tissue.
- * Only PI abnormality - acute arterial occlusion but no infarct (keir - 84)

MR ANGIOGRAPHY

MR angiography enables the noninvasive evaluation of vascular patency. Images can be generated on which flow within the vessel is increased in signal intensity (bright blood) or on which the lumen is depicted as decreased in signal intensity (black blood); the former is the more commonly used technique. Time of flight is the most frequently used bright-blood MR angiographic technique. For evaluation the intracranial circulation, a volumetric (three-dimensional) acquisition is optimal.

An image similar to a conventional arteriogram can be reconstructed from the intravascular signals that is sensitive to large vessel occlusion or narrowing in the internal carotid, vertebral, basilar and first and second segments of the anterior, middle and posterior cerebral arteries. Although the value of MR angiography has yet to be shown in a large-scale clinical trial, the need for differentiating

which patients have lesions amenable to thrombolysis seems clear given the potential risks of treatment.

MR SPECTROSCOPY

In the evaluation of patients with cerebral ischemia the relevant metabolites are lactate at 1.33 parts per million (ppm) and N-acetylaspartate (NAA) at 2.02 ppm. Lactate is not present in sufficiently high concentrations to measure in the brain under normal conditions. NAA is normally present and is found only in neurons or axons in mature brain¹.

MR spectroscopy depicts acute cerebral ischemia on the basis of increased levels of lactate. NAA decreases after the onset of either global or focal ischemia. NAA is either dramatically reduced or completely absent. It is postulated that in acute stroke, tissue that has high lactate, no conventional MR imaging abnormalities and normal or only slightly reduced NAA levels in the first few hours after stroke onset may represent ischemic tissue at risk of infarction. This issue could represent the "penumbra". It has been hypothesized that identification of such regions may, in the future, may be one of the criteria for initiating thrombolytic therapy¹.

Limitations of MRS : (1) Proton MR spectroscopic imaging is not able to detect lacunar or small infarcts (<1 cm³). The higher spatial resolution of diffusion and perfusion MR imaging is definitely an advantage in this regard. (2) The implementation of MR spectroscopic imaging is hampered by the limited coverage and lengthy imaging times.

DSA AND THROMBOLYSIS

DSA (Digital Subtraction Angiography) is the gold standard for delineation of arterial architecture and site of occlusion of artery. With improvement in technique it is now safer and effective in treating the selected patients with stroke with intra arterial thrombolysis in window period of 6 hours. Prompt reestablishment of flow with lysis of an occlusive thrombus is the goal of thrombolysis. It can be done either by intra venous route or direct intra arterial injection of thrombolytic agent. This is in contrast to anticoagulation, in which new clot formation is minimized. These agents convert the proenzyme plasminogen to the active enzyme in thrombin lysis, plasmin. Thrombolysis can be performed by using streptokinase, urokinase or rt-PA, rt-PA is the most specific of the three agents. It is fibrin specific, activating only thrombin-bound plasminogen. For this reason, it has the most favourable therapeutic index of the three thrombolytic agents.

Thrombolysis was introduced for the treatment of ischemic lesions of the middle cerebral artery (MCA) territory. Thrombolytic agents were used to treat acute ischemia within 3-6 hours after the acute event. This risk increased as the time interval between the onset of symptoms and thrombolytic therapy increased. Thus, patients are more likely to have a good outcome when treated within 3 hours than between 3 and 6 hours after the acute event. Therefore, the primary purpose of diagnostic imaging is to ensure selection of the appropriate patients for thrombolytic therapy to reduce severe complications¹.

For this purpose, diagnostic imaging of acute stroke should reliably help (a) exclude intracranial hemorrhage; (b) differentiate between irreversible affected brain tissue ("dead brain") and reversibly impaired tissue ("tissue at risk"), which might benefit from early

treatment and (c) identify stenosis or occlusion of major extra and intracranial arteries.

Tissue at risk, or "penumbra," is defined as an area of markedly reduced perfusion with loss of function of still viable neurons¹. Timely reperfusion of this tissue may prevent cell death and help reestablish normal function. Because thrombolysis of large areas of irreversibly affected brain tissue carries a high risk of hemorrhage, patients with infarction that affects more than one-third of the MCA territory should not undergo thrombolysis.

The NINDS (National Institute for Neurological Diseases and Stroke) trial was the first trial to demonstrate efficacy in the use of the thrombolytics for the treatment of cerebral ischemia². The protocol was based on a 3-hour treatment window from the time of iclus to the administration of rt-PA. A CT scan was obtained and the detection of intracerebral thrombosis was an exclusion criterion. Although no short-term benefits were demonstrated, patients in the treatment group achieved improved stroke scale ratings as compared with those in the placebo group at 3 months. *The ECASS (European Cooperative Acute Stroke Study) is another trial* which allowed a longer treatment window of 6 hours¹⁸. This time-window prolongation increased the likelihood of manifest infarction at the time of reestablishing flow and thus the risk of reperfusion hemorrhage. In an attempt to avoid reperfusion hemorrhage, a CT scan was obtained to exclude patients with extensive infarction. Patients were excluded if on site interpretation detected infarction in greater than 33% of the middle cerebral artery (MCA) distribution. Unfortunately, the ECASS group failed to demonstrate efficacy in the intention to treat group.

Recent advances in techniques of intracranial vascular catheterisation have made it possible to deliver thrombolytic agents intraarterially directly proximal to the thrombus with much less systemic side effects¹⁹.

Limitations of DSA and Thrombolytic Therapy : The major disadvantage of intraarterial thrombolytic therapy is that it can only be undertaken in centers where neurointerventional specialists and infrastructure required for this intervention are available. Furthermore, the administration of a potentially toxic drug by a highly specialized technique to an acutely ill and vulnerable patient within a short time frame demand an expert decision making process after a thorough consideration of the risks and benefits. Because of these reasons, it is unlikely that selective intraarterial thrombolytic therapy will ever produce a significant impact in the treatment of acute ischaemic stroke in a developing country¹⁹.

In summary, acute ischemic stroke is prominent cause of death and morbidity. It needs to be identified by the clinician and the radiologist at the earliest, so as to start appropriate treatment immediately. The main role of CT scan is to rule out hemorrhagic stroke, however can be clubbed with CTA and CT perfusion study for better characterization of the site and extent of lesion. MR imaging proves to be a better modality as can detect changes as early as 3 hours with advent of newer imaging techniques like diffusion and perfusion imaging and supportive role of MRA and MRS. With appropriate patient selection, intra venous thrombolysis can be done within 3 hours of onset of symptoms and with help of DSA, intra-arterial thrombolytic agents can be used in window period of 6 hours in anterior circulation. Experience and expertise is required to carry out such procedure.

REFERENCES

1. *Beauchamp, NJ Jr; Baker, PB; Wang, PY, et al.* Imaging of acute cerebral ischemia. *Radiology.* 1999;212(2):307-24 Review
2. *National Institute of Neurological Disease and Stroke rt-PA Study Group.* Tissue plasminogen activator for acute ischemic stroke. *N. Engl. J. Med.* 1995;355:1581-1587
3. *Klatzo, I.* Neuropathological aspects of brain edema. *J. Neuropathol. Exp. Neurol.* 1967;26:1-14
4. *Truwit, CL; Barkovich, AJ; Gean-Martin, A; et al.* Loss of the insular ribbon : another sign of CT infarction. *Radiology.* 1990;176:801-806
5. *Tomura, N; Uemura, K; Inugami, A; et al.* Early CT finding in cerebral infarction : obscuration of the lentiform nucleus. *Radiology.* 1988;168:463-467
6. *Bryan, RN; Levy, LM; Whitlow, WD; et al.* Diagnosis of acute cerebral infarction : comparison of CT and MR imaging. *AJNR.* 1991;12:611-620
7. *Leys, D; Pruvo, JP; Godefroy, O; et al.* Prevalence and significance of hyperdense middle cerebral artery in acute stroke. *Stroke* 1992;23:317-324
8. *Wing, SD; Norman, D; Pollock, JA; et al.* Contrast enhancement of cerebral infarcts in computed tomography. *Radiology* 1976;121:89-92
9. *Becker, H; Desch, H; Hacker, H; et al.* CT fogging effect with ischemic cerebral infarcts. *Neuroradiology.* 1979;18:185-192
10. *Fisher, M; Pessin, MS; Furian, AJ; et al.* Lessons for future thrombolytic stroke trials. *European Cooperative Acute Stroke Study (editorial).* *JAMA* 1995;274:1058-1059
11. *Meuli, RA.* Imaging viable brain tissue with CT scan during acute stroke. *Cerebrovas. Dis.* 2004;17(Suppl.3):28-34
12. *Miles, KA; Griffiths, MR.* Perfusion CT : a worthwhile enhancement? *Br. J. Radiol.* 2003;76(904):220-31
13. *Shrier, DA; Tanaka, H; Numaguchi, Y; et al.* CT angiography in the evaluation of acute stroke. *AJNR Am. J. Neuroradiol.* 1997;18(6):1011-20
14. *Schellinger, PD; Jansen, O; Fiebich, JB; et al.* A standardized MRI stroke protocol : comparison with CT in hyperacute intracerebral hemorrhage. *Stroke.* 1999;30(4):765-8
15. *Lee, LJ; Kidwell, CS; Alger, J; et al.* Impact on stroke subtype diagnosis of early diffusion weighted magnetic resonance imaging and magnetic resonance angiography. *Stroke.* 2003;31(5):1081-9
16. *Bryan, RN; Levy, LM; Whitlow, WD; et al.* Diagnosis of acute cerebral infarction : comparison of CT and MR imaging. *AJNR.* 1991;12:611-620
17. *Elster, AD; Moody, DM.* Early cerebral infarction : gadopentetate dimeglumine enhancement. *Radiology.* 1990;177:627-632
18. *Hacke, W; Kaste, M; Fieschi, C; et al.* for the ECASS Study Group. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemisphere stroke : the European Cooperative Acute Stroke Study. *JAMA.* 1995;274:1017-1025
19. *Sylaja, PN; Kuruttukulam, G; Joseph, S; et al.* Selective intra arterial thrombolysis in acute carotid territory stroke. *Neurol. India.* 2001;49(2):153-7

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DRUG PROFILE

CILOSTAZOL

Cilostazol is quinolin derivative; - its metabolites are cyclic AMP (cAMP) phosphodiesterase 111 inhibitors (PDE III inhibitors). Inhibition of phosphodiesterase activity suppresses cAMP degradation with a resultant increase in cAMP in platelets and blood vessels leading to inhibition of platelet aggregation and vasodilatation, respectively. It reversibly inhibits platelet aggregation induced by a variety of stimuli, including thrombin, ADP, collagen, arachidonic acid, epinephrine and stress. It produces non-homogenous dilatation of vascular beds with greater dilatation in femoral beds than in vertebral, carotid or superior mesenteric arteries.

Pharmacokinetics : It is absorbed after oral administration; it is 95-98% protein bound, and extensively metabolized by hepatic cytochrome P-450 enzymes. The primary route of elimination of cilostazol is via the urine (74%) with the remainder excreted in the feces (20%). The total pharmacologic

activity of drug and its metabolites is similar with mild renal and hepatic impairment and also in normal subjects.

Indications : Cilostazol is indicated for the *reduction of symptoms of intermittent claudication*; improves pain free and maximal walking distance, has favourable effects on lipids.

Dosage and administration : Recommended dosage of drug is 100 mg BD, to be taken half an hour before meals or two hours after food.

Contra-indication : a) Contraindications are hypersensitivity to the drug; b) congestive heart failure of any severity; c) pregnancy and d) nursing mothers and children.

Adverse reactions : Commonly observed side effects include headache, diarrhoea, dizziness and palpitations, overdosage may cause headache, diarrhoea, hypotension, tachycardia, arrhythmia, not removed by dialysis.

Cardiovascular effects : Increased heart rate, ventricular premature complexes, non sustained VT is reported.

Compiled by Dr. .P.Chattree