



The Cardiac Society of Australia and New Zealand

Safety and Performance Guidelines for Pharmacologic Stress Testing in Conjunction with Clinical Cardiac Imaging Procedures

Background

This document has been prepared conjointly by a committee representing both the Cardiac Society of Australia and New Zealand (CSANZ) and the Australia and New Zealand Association of Physicians in Nuclear Medicine (ANZAPNM). It complements the previously published “*Safety and Performance Guidelines for Clinical Exercise Stress Testing.*”

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1. Introduction

These guidelines complement those previously published for clinical exercise stress testing. Whilst the general principles underlying the safe and effective performance of stress testing are common to both exercise and pharmacologic approaches, this document addresses issues *specific* to the use of pharmacologic agents for cardiac stress testing in conjunction with clinical imaging procedures. Such procedures include perfusion imaging (scintigraphy) and imaging of left ventricular function (echocardiography and gated cardiac blood pool scintigraphy).

Exercise testing remains the preferred method of stress employed for routine cardiac stress examinations whenever possible. However, pharmacologic stress testing in combination with cardiac imaging has emerged as an alternative method for the evaluation of known or suspected coronary artery disease in patients unable to achieve a diagnostic endpoint during exercise testing.

Clinical stress protocols for both vasodilators (dipyridamole and adenosine) as well as the synthetic catecholamine dobutamine (in combination with atropine) are presented.

The stress testing protocols for diagnostic imaging are most widely employed for the diagnosis and/or characterisation of patterns of coronary artery disease in patients with suspected or known CAD. They may also be employed where appropriate for the evaluation of myocardial viability. However in this setting there may be limitations to the use of maximal exercise or inotropic stimulation protocols in the presence of advanced left ventricular dysfunction or associated rhythm disorders. While vasodilator stress can usually be employed to image the results of flow heterogeneity short of inducing ischaemia, in a minority of patients they can induce ischaemia which may acutely worsen already impaired left ventricular function in such patients. For radionuclide studies with both SPECT and PET tracers, viability studies can be performed at rest, with no need for a stress test.

The efficacy of these pharmacologic approaches in regard to the diagnostic information obtained from the associated imaging procedures has been documented as similar to those using maximal exercise stress studies. There are also some specific instances where pharmacologic stress may be the initial preferred method of stress testing for imaging procedures e.g. perfusion imaging using dipyridamole stress in patients with left bundle branch block or low-dose dobutamine echocardiography for myocardial viability assessment.

Personnel should be experienced in the selection of appropriate stress agents for the individual patient and the clinical question being asked.

The risks associated with pharmacologic stress testing are also similar to those documented for exercise stress. Thus, death can occur once in every 2000 to 3000 patients tested, depending on the patient population being tested. Non fatal infarction is reported to occur once every 1000 to 2000 patients tested. Unstable angina pectoris, systemic hypotension, heart failure, and serious arrhythmias can also occur during testing and the skills and facilities to promptly recognise and treat such complications are essential in every laboratory. In view of these risks the medical practitioner responsible for stress testing should obtain informed consent prior to pharmacologic stress testing.

Individual pharmacologic stress agents also have well documented contraindications. Personnel should be experienced in excluding patients from the use of a particular pharmacologic stress agent in the presence of such a contraindication.

2. Stress Testing

Physical Environment

Sufficient physical space is required for the safe and comfortable conduct of the stress protocol and the timely treatment of any complications. Pharmacologic studies are usually performed with the patient lying supine on a bed. Resuscitation equipment must be located in the same room with sufficient space for cardiopulmonary resuscitation to be effectively performed. Equipment for the use of supplemental exercise with dipyridamole or adenosine (treadmill or cycle ergometer) should also be in the same room.

Stress Equipment

The intravenous use of the short-acting receptor agonists adenosine and dobutamine requires the use of a controlled delivery infusion device. Individual devices require Therapeutic Goods Administration approval and must conform to Australian Standard AS3201.1 for electrical safety. All such devices should be periodically checked for accurate volume delivery performance.

Exercise devices used in conjunction with pharmacologic stress (motorised treadmills or braked cycle ergometers) should comply with the description given in paragraph 2b) of the *Safety and Performance Guidelines for Clinical Exercise Stress Testing*.

All equipment should be well maintained and checked for performance and safety regularly.

Recording of Stress Parameters

With dobutamine stress target heart rate may be calculated from an appropriate nomogram (*or as below under "Dobutamine"*) and recorded on a patient worksheet prior to protocol commencement. With vasodilator stress this is required only if supplemental exercise is to be employed.

A permanent medical record of the test details (including patient's name, date, test indication, relevant history including medications and prior drug reactions, recent caffeine consumption, heart rate and blood pressure measurements during stress, symptoms during and post-stress, presence and quality of any chest pain, any side effects, any untoward effects, ECG interpretation for ischaemia and arrhythmias, total doses of all drugs administered and copies of the electrocardiographic recordings) should be made.

Electrocardiographic Monitoring

Preparation

Adequate skin preparation and electrode fixation (whether adhesive or suction based) is required to ensure good skin contact and artifact-free signal quality. This requires alcohol cleaning to remove oil and skin preparation with a disposable abrasive device to remove dead horny layer cells. The applied electrodes should be tested for good skin contact by performing an ECG tracing and making adjustments prior to the stress test.

Baseline Electrocardiogram

A standard 12 lead electrocardiogram should be obtained and printed out with the patient supine using a 3 channel ECG machine with appropriate low frequency filters and phase response for accurate recording. An additional modified trace with the limb leads repositioned on the torso should also be recorded if supplemental exercise is to be used. An upright trace should be obtained prior to commencing supplemental exercise. Before proceeding with the stress study the physician should compare the baseline ECG with any previous ECG when possible.

Recordings During Pharmacologic Stress

The 12 lead ECG should be continuously monitored on a video display screen during the stress protocol to detect ischaemia and arrhythmias. Continuous display of three leads including an inferior lead, V5 and V1 or V2 is required to adequately detect ECG changes of ischaemia. Further 12 lead print out should be obtained during each stage of the stress protocol or at least every three minutes. Additional 12 lead print outs should be obtained at the end of the stress protocol.

ECG monitors should have memory to enable capture and later print out of abnormal cardiac rhythms.

Computerised ECG systems which have signal averaging included still require the raw trace to be printed out and visually interpreted to avoid incorrect computer interpretation of heart rate or ST segments due to either noise or artifact.

ECG Recordings During Recovery Period

12 lead hard copy should be obtained twice during the recovery period which should routinely last at least five minutes, unless the imaging protocol necessitates a shorter period (as is the case with thallium-201 imaging). Additional recordings in recovery should be obtained to document recovery from ischaemia or arrhythmia as necessary. Should imaging need to be performed prior to the ECG reverting to the pre test configuration then a delayed trace following imaging is required.

Blood Pressure Measurement

A sphygmomanometer is required to record baseline systolic/diastolic blood pressure as well as measurements during each stage of the stress protocol or at least once every three minutes. Measurements should be made at least twice following stress and for longer periods as required to document return of blood pressure to the pre test level. Repeat measurement following completion of scintigraphy may be required as for "*ECG Recordings During Recovery Period*" above.

Recording of Symptoms and Documentation

The presence, quality and severity of chest pain, breathlessness, dizziness, fatigue and other symptoms including those related to the pharmacologic stress agent (e.g. burning, flushing, light-headedness, apprehension) should be recorded by the physician based on direct questioning during the stress period. Recovery and any treatment required should also be documented.

Resuscitation Equipment

All laboratories using pharmacologic stress testing must be able to provide advanced cardiac life support on-site. Equipment required for this must be maintained and checked regularly and includes:

i) Defibrillator:

Must comply with Australia/New Zealand standard A/NZS 3204 and maintained/tested regularly as specified in A/NZS 3551 "*Procurement, acceptance, safety and functional testing of active medical devices.*" Conductive gel or gel pads must be available and the defibrillator able to be manoeuvred into place for effective patient treatment in the stress room.

ii) Suction:

Motor or gas driven suction with extension tubing and attachable suckers for clearing the airway of the patient must be available in the laboratory.

iii) Airway plus self-inflating bag:

Plastic or rubber self-inflating bag and patient airways for the ventilation of a patient during cardiac arrest are required in the laboratory and must be regularly checked and maintained.

iv) Oxygen:

Cylinder or wall-mounted oxygen supply with appropriate tubing and masks for delivery to the patient are required.

v) Drugs and intravenous administration equipment:

Equipment for the sterile placement and maintenance of intravenous lines is required. Together with the pharmacologic stress agents, other drugs and intravenous fluids must be kept in the laboratory. These include: atropine, lignocaine, adrenaline and sotalol or amiodarone, together with sublingual nitroglycerin tablets and/or spray. Salbutamol or other beta-2-agonist metered aerosol for bronchospasm is required. Aminophylline is needed to antagonise the effects of dipyridamole. Esmolol is a short acting beta adrenergic receptor blocker which has been used to antagonise the effects of dobutamine. Intravenous 0.9% saline or 5% glucose may be required to treat hypotension associated with pharmacologic stress. All supplies must be checked regularly and in date.

Communications and Alarm

All laboratories require an alarm system to raise the help of nearby personnel promptly and a telephone for contacting an intensive care ambulance in an emergency.

3. Imaging Equipment

The imaging equipment and protocols for its use should be well maintained and capable of providing diagnostic imaging information in keeping with any clinical practice guidelines currently in place.

In the case of nuclear imaging the gamma camera used should have gated SPECT capability and the capacity to provide diagnostic quality images for the radiotracer being used, either thallium-201 or a technetium-99m flow tracer. Camera performance should be monitored with a regular quality control testing programme.

For echocardiography there should be the capacity for image frame-grabbing and simultaneous loop display of images at rest and multiple levels of stress. Such simultaneous display of cine loops facilitates accurate assessment of wall motion abnormalities and changes developing at different phases of the study. The assessment of wall motion abnormalities can be facilitated by a number of improvements in technology, including harmonic imaging, administration of contrast agents, strain rate imaging, etc.

4. Personnel

Two persons trained in cardiopulmonary resuscitation should be present in the stress room at all times for patient safety. They should be trained in recognition of the major arrhythmias and ischaemic patterns on the electrocardiogram. At least one should be a suitably qualified medical practitioner registered in the state in which the laboratory is situated.

Medical Practitioner

The medical practitioner responsible for overseeing the pharmacologic stress test must have a medical qualification and be currently registered by the appropriate medical board. The medical practitioner must be in attendance in the room during pharmacologic stress and during the immediate post-stress period. The medical practitioner must have competence and abilities in the following specific areas:

Indications and Contraindications for Pharmacologic Stress

The medical practitioner through obtaining an appropriate history and physical examination in conjunction with information from the referring medical practitioner must be able to determine that pharmacologic stress using a particular stress agent is appropriate for the individual patient to assist in answering the clinical question being asked and that there are no contraindications to the use of that agent. The medical practitioner must further be able to take into account any individual circumstances which may indicate the need for special precautions to be taken in the use of a particular agent in a given patient.

ECG Interpretation

The medical practitioner must be able to interpret all the major abnormalities which can be detected on 12 lead electrocardiography, in particular those related to ischaemic heart disease. This includes abnormalities on the resting trace likely to preclude the interpretation of the stress ECG, and those which might determine that testing be cancelled or deferred. The practitioner should also be able to recognise all the major arrhythmias and ECG patterns indicating myocardial ischaemia during testing and to interpret the ECG traces for the presence or absence of ischaemia at the completion of testing.

Interpretation of Symptoms

The practitioner should be able to recognise the significance of all symptoms occurring during pharmacologic stress testing and to differentiate ischaemic from non-ischaemic symptoms.

Basic and Advanced Life Support

The supervising medical practitioner must be fully versed in the techniques of basic and advanced life support (as defined by the Australian Resuscitation Council or in the New Zealand Standards and Guidelines on Basic Life Support) and be able to perform these skills in an emergency. These skills include ability to diagnose the cause of the underlying problem and to apply early rapid defibrillation to the patient, to perform external cardiac massage, to ventilate the patient using airway and bag with mask, to cannulate the patient and administer the drugs detailed above appropriately.

The practitioner should be able to demonstrate continuing competence in resuscitation for example by second annual attendance at retraining courses.

Experience in clinical pharmacologic stress testing

The practitioner should have sufficient knowledge to safely conduct and accurately interpret the pharmacologic stress studies. This includes knowledge regarding selection of agent, contraindications, pharmacologic and clinical effects of the agent, administration protocols, adverse effects, reversal of pharmacologic effect, drug interactions, and when to terminate the pharmacologic stress period.

Assistant for Pharmacologic Stress testing

The second person should be a health professional from a background including the following: nurses, technologists or their equivalent, other suitably qualified health professionals. The minimum required skills include:

- ability to perform cardiopulmonary resuscitation;
- ability to obtain a high quality ECG trace at rest and during stress;
- ability to recognise the major arrhythmias and ischaemic ECG changes and clinical manifestations likely to occur during pharmacologic stress testing.

Further details are included in the *“Safety and Performance Guidelines for Clinical Exercise Stress Testing”*.

Withholding of medication

As with exercise testing, ideally anti-anginal medication, particularly beta-blockers, should be withheld for up to 48 hours prior to the test to maximise test sensitivity and avoid potential underestimation of true extent of ischaemia. There is a small clinical risk of acute coronary syndrome associated with abrupt withdrawal of beta blockers in patients with coronary artery disease so this needs to be modified according to each individual patient, and in certain cases, the test can be performed on anti-anginal medications. Also, PDE 5 inhibitors (e.g. sildenafil, vardenafil and tadalafil), used for erectile dysfunction and also for pulmonary arterial hypertension, should be withheld for 48 hours prior to the test, in case nitrates are required during the study. Ideally, the opinion of the referring Doctor should be sought in regard to cessation of therapy in these situations.

5. Pharmacologic Stress Protocols

Details of the commonly employed clinical protocols for the conduct of pharmacologic stress testing together with appropriate background information follow. The techniques are most commonly employed in the diagnosis or evaluation of coronary artery disease. Special protocols are also in use to evaluate myocardial viability in some patients.

Vasodilator Stress

Vasodilators are the most widely studied and currently preferred agents for use in conjunction with perfusion imaging. They increase blood flow (and hence the degree of flow heterogeneity during induced hyperaemia in patients with coronary artery disease) more than dobutamine. They are however considered second line agents after dobutamine for imaging of LV function (as they induce fewer abnormalities of regional wall motion and thickening).

Electrocardiographic evidence of myocardial ischaemia is produced in a relatively small proportion of patients with this form of stress (usually those with severe multivessel coronary artery disease dependent on collateral flow).

Whilst adenosine may have some theoretical advantages over dipyridamole by virtue of its direct action, current data suggest similar safety and efficacy profiles overall for both dipyridamole and adenosine in clinical use.

i) Dipyridamole

Rationale for Use

This agent creates regional heterogeneity in coronary artery flow reserve in patients with coronary artery disease. This heterogeneity can be imaged as a stress-induced perfusion defect on scintigraphic images. It can also be used for echocardiography or blood pool imaging in patients unsuited to dobutamine stress. Dipyridamole stress-induced regional wall motion abnormalities are imaged in order to detect the presence of coronary artery disease with this approach. As with other pharmacological agents, it can be used in patients unable to exercise and in those clinically stable at least 48 hours post myocardial infarction. Dipyridamole and adenosine should also be considered in patients with left bundle branch block as vasodilator stress is associated with fewer septal artefacts than exercise stress.

Mechanism of Action

Dipyridamole is a lipophilic pyrimidine. Its administration leads to arteriolar vasodilatation through inhibition of phosphodiesterase which in turn inhibits reuptake of endogenously produced adenosine into endothelial and red blood cells. This increases coronary arterial flow to approximately three times resting values in normal subjects. Hyperaemic flow is attenuated in tissue supplied by a stenosed coronary artery. This leads to heterogeneity of tracer uptake on perfusion images or new regional wall motion abnormalities on imaging of left ventricular function.

There is usually a modest reflex increase in heart rate secondary to a mild decrease in systolic blood pressure. 15% of patients can exhibit a rise in blood pressure however.

Pharmacokinetics

Maximal vasodilatation is achieved approximately three minutes following completion of the four minute infusion. Effects on the circulation peak from 7 to 12 minutes and then gradually dissipate over the next 10 to 15 minutes. Symptoms and/or haemodynamic effects can still be evident at 30 minutes in a very small proportion of patients.

Administration

Dipyridamole is administered intravenously at a standard dose of 0.56mg/kg over 4 minutes. An infusion delivery device is not required. Tracer is injected during peak hyperaemia at 7 minutes from commencement of injection. Higher doses up to 0.84mg/kg have been employed with echocardiography to achieve a small diagnostic gain. There are more minor side effects but no substantial difference in safety profile. Higher doses have been less widely studied with perfusion imaging.

Supplemental exercise (used with perfusion imaging to increase relative cardiac vs. hepatic uptake of flow tracer to enhance image quality) is performed immediately following dipyridamole administration and should be completed within 8 minutes so tracer injection is performed during the period of peak hyperaemia.

Dipyridamole may increase the effects of antihypertensive drugs. Dehydration should be avoided in patients scheduled for dipyridamole stress studies.

Adverse Effects

In 3911 patients studied with 0.56mg/kg/min 47% experienced one or more side effects:

Major

Fatal MI in multicentre registries, adenosine and dipyridamole administration are associated with a 0.0001% acute cardiac death rate

Nonfatal MI 0.05%

Bronchospasm 0.15%

Other

Chest pain 20%

Dizziness 12%

Dyspnoea 3%

Flushing 3%

Nausea 5%

Headache 12%

Hypotension 5%

Palpitation 3%

ST segment changes 8%

Transient ischaemic attack has been reported in one patient with cerebrovascular disease.

Transient asystole has been reported in subjects without coronary artery disease not receiving beta adrenergic blockers during administration of intravenous dipyridamole performed concurrently with erect bicycle exercise.

Reversal of Effects

The effects of dipyridamole may be antagonised by intravenous aminophylline in incremental doses of 25mgs by intravenous injection up to 250mgs as required. Aminophylline is a competitive inhibitor of phosphodiesterase. It has a shorter half-life than dipyridamole so later repeat injection of aminophylline is sometimes required. There are no data to demonstrate a benefit of routine vs. selected administration for effects such as ischaemia, hypotension, rhythm disturbance (atrioventricular block rarely) or symptoms of discomfort (usual reason).

Ischaemia is usually relieved by aminophylline and oxygen, with other agents if required (nitrates).

Specific contraindications

Within 48 hours of acute myocardial infarction

Unstable angina with rest pain within last 48 hours

Severe lung disease or asthma

Heart failure/severe LV systolic dysfunction

Second or Third Degree Atrioventricular block without a pacemaker

Resting hypotension

Prior adverse reaction to dipyridamole

Drug interactions

False negative dipyridamole stress perfusion studies have been clearly demonstrated in patients with coronary artery disease who have had recent intake of caffeine. Caffeine and other methylxanthines (aminophylline, theophylline) should be ceased for an adequate period prior to testing (most laboratories require a minimum period of at least 24 hours and many 48 hours). In patients not exhibiting a haemodynamic response to the standard dose of dipyridamole, caffeine consumption prior to testing may have occurred. Such patients may require repeat testing after abstinence from caffeine or the use of an alternate method of cardiac stress testing.

Beta adrenergic blockers: Marked bradycardia has been reported with vasodilator administration in patients on background beta adrenergic blocker therapy.

Patients receiving chronic oral dipyridamole may fail to show an acute haemodynamic response to intravenous dipyridamole: In this situation, cessation of oral dipyridamole for 48-72 hours prior to testing is recommended.

ii) Adenosine

Rational for Use

see above for Dipyridamole

Mechanism of Action

Adenosine is an endogenous nucleoside produced within the arterial vascular bed. It acts via specific G-protein-coupled adenosine receptors. The resulting vasodilatation is more potent and consistent than with dipyridamole.

Pharmacokinetics

It is a receptor agonist with a rapid onset of action (within seconds). Its elimination half-life is a few seconds. This is by carrier-mediated uptake and subsequent metabolism by adenosine deaminase.

Administration

Adenosine is very potent and requires the use of a controlled delivery infusion system. It is usually given as a constant infusion at a dose of 140mcg/kg/minute. It is helpful to prepare a chart converting the adenosine dose into the infusion rate required, according to the patient's weight.

A graded infusion commencing at 70mcg/kg/minute increasing to 100 and then 140mcg/kg/minute each minute to the maximum tolerated dose rate has been advocated for higher risk patients. However lower peak infusion rates are likely to reduce test diagnostic performance.

For perfusion imaging the recommended duration of administration is six minutes with tracer injection at 3 minutes into the infusion. There is less evidence available concerning diagnostic accuracy with a 4 minute infusion protocol. A separate intravenous line or T-piece system is required for tracer injection to avoid an adenosine bolus effect which has been demonstrated to sometimes result in acute transient high-grade atrioventricular block.

Adenosine can be combined with an exercise protocol to improve image quality.

Adverse Effects

Overall these are similar to dipyridamole. There is a higher proportion of symptoms (81%) but they terminate rapidly on cessation of the infusion. Atrioventricular block is more common than with dipyridamole but is usually asymptomatic and reversible.

In 9256 patients 81% experienced one or more side effects:

Major

Fatal MI 0%

Nonfatal MI 0.01% (highlighted in case reports)

Bronchospasm 0.07%

Other

Palpitation 7.6% (atrioventricular block, usually asymptomatic)

Chest pain 35%

Flushing 37%

Headache 14%

Shortness of breath 35%

Epigastric discomfort 9%

Nausea 15%

Dizziness 9%

ST segment changes 6%

Reversal of Effects

Due to its very short half-life the effects of adenosine are usually rapidly reversible upon cessation of infusion. Aminophylline injection is rarely if ever required. Ischaemia is treated with nitroglycerine and oxygen.

Specific contraindications

Resting hypotension

Asthma

Heart failure

Second or Third Degree Atrioventricular block without pacemaker

Atrial fibrillation with uncontrolled ventricular rate

Prior adverse reaction to adenosine

Caution should be exhibited in liver transplant candidates with advanced hepatic dysfunction and/or anaemia and liver transplant recipients with graft failure due to an increased incidence of sinus arrest related to impaired adenosine metabolism.

Drug Interactions

as for dipyridamole above

Dobutamine Stress

Rationale for Use

Dobutamine is a synthetic catecholamine. This is the preferred pharmacologic stress agent when imaging of cardiac function (echo, blood pool scintigraphy) is being performed. By way of comparison, dobutamine is more effective in producing stress-induced regional wall motion abnormalities, while vasodilator stress results in greater increase and regional heterogeneity of blood flow.

Dobutamine produces myocardial ischaemia by increasing determinants of myocardial oxygen demand including heart rate, blood pressure and contractility. In myocardium supplied by a stenosed coronary artery, the increase in oxygen demand cannot be met by an adequate increase in blood flow, leading to regional wall motion abnormalities or flow heterogeneity.

Compared with exercise, dobutamine produces a greater increase in inotropic state and less increase in heart rate, with a variable effect on blood pressure. Dobutamine produces ischaemia at a lower rate-pressure product than exercise, indicating the contribution of increased contractility.

Candidates for dobutamine stress with perfusion imaging represent a higher risk group as they are likely to have significant co-morbidities which have ruled them out for exercise or vasodilator stress. The imaging findings available with echocardiography together with dobutamine stress which may lead to early test termination (see below) are not available with radionuclide perfusion imaging.

Mechanism of Action

Dobutamine is a short-acting synthetic catecholamine with beta-1 agonist and some beta-2 agonist and alpha effects. Dobutamine is positively inotropic, increasing stroke volume and cardiac output at clinical doses. It also exerts a chronotropic effect but this is variable between patients and is in any case less than that of other catecholamines (e.g. isoprenaline). At higher doses hypotension is frequently observed during clinical stress testing presumably related to the alpha-1 and beta-2 receptor mediated vasodilatation.

Since the heart rate increase with dobutamine is modest, atropine supplementation is frequently utilised during stress testing (*see below*).

It is metabolised via methylation and conjugation and eliminated by both renal and biliary routes.

Pharmacokinetics

Dobutamine has a half life of two minutes. Steady state is achieved after ten minutes. Plasma concentrations appear to be linearly related to infusion rates over the range studied clinically. The elimination half life of dobutamine is less than three minutes.

Administration

Target heart rate is determined from a nomogram or calculated as $(220 - \text{age in years})$. Dobutamine is administered in diluted form as a continuous intravenous infusion via a programmable controlled infusion delivery device capable of accurate volume delivery and prompt stepwise increments in rate of administration during infusion. The patient intravenous tubing should have the minimum possible dead space to avoid any lag effect following dose increments. It is helpful to prepare a chart converting the -dobutamine dose at various stages into the infusion rate required at each stage, according to the patient's weight.

The infusion protocol consists of 3 minute stages at incremental doses of 5, 10, 20, 30, 40 and if necessary 50 mcg/kg/minute. If 85% predicted heart rate response is not achieved with this protocol and a diagnostic ECG or echocardiographic endpoint has not been reached then atropine may be added (*see below*). Conversely, the infusion may be terminated early upon attaining such a diagnostic endpoint at a lower dose rate.

The infusion should be terminated at any time if there is clinical, ECG or echocardiographic evidence of moderate to severe ischaemia, or if major adverse effects occur.

For nuclear studies tracer injection is performed at least one minute prior to infusion termination. Care to avoid a bolus effect (*see "Adenosine," above*) is important and usually requires use of a separate intravenous line or at least 2 ports or three-way taps.

Particular care should be taken to avoid dobutamine extravasation into tissues (*see below under "Reversal of Effects"*) which requires termination of infusion, withdrawal of intravenous cannula, limb elevation, and consideration of phentolamine administration (5-10 mg, diluted in 10 ml saline injected with a fine needle into the region of extravasation).

Adverse Effects

The main adverse effects are hypotension and arrhythmias. Both are dose related. Non-cardiac adverse effects are common but rarely require interruption of the test. These effects include nausea, anxiety, headache, tremor, palpitation, presyncope, urgency and chills.

In 1118 patients 35% had one or more side effects:

Major

Nonfatal MI 0.1%

Other

Palpitation 35% (tachyarrhythmias)

Anxiety 6%

Chest pain 19%

Dyspnoea 5%

Headache 4%

Hypotension 3%

Nausea 8%

Tremor 4%

ST segment changes 9% (coronary artery spasm with ST segment elevation can occasionally occur, for which nitrate therapy may be preferable to beta-blockade)

Serious Arrhythmias in 5817 patients in 4 studies

Ventricular Fibrillation 0.05%

Sustained ventricular tachycardia 0.2%

Non sustained ventricular tachycardia 4%

Supraventricular arrhythmias 3%

Death: two deaths have been reported with dobutamine stress imaging studies in 1997

Hypotension

In contrast to exercise testing, hypotension during dobutamine infusion is not usually a marker of severe ischaemia or severe left ventricular dysfunction. Possible mechanisms of dobutamine induced hypotension include ischaemic left ventricular dysfunction, systemic vasodilator effect of dobutamine, dynamic left ventricular outflow tract dysfunction, and vasodepressor reflex (Bezold-Jarisch).

The latter two mechanisms are supported by the finding that hypotension occurs less frequently in patients taking beta-blockers and more frequently in patients with high resting left ventricular ejection fraction or with high resting systolic blood pressure. Left ventricular dysfunction and dynamic left ventricular outflow tract dysfunction can be diagnosed by two-dimensional and Doppler echocardiography during the dobutamine infusion.

Dobutamine infusion should be ceased if hypotension is severe, e.g. < 80-100 mm Hg systolic or >40 mm Hg decline, or if hypotension is progressive, symptomatic or associated with evidence of severe ischaemia. Infusion should also be stopped if echocardiographic imaging demonstrates intracardiac gradients >3-3.5 m/s, often associated with LV cavity obliteration or marked systolic anterior motion of the mitral valve. If left ventricular function appears hyperdynamic and the ventricle appears hypovolaemic at baseline, infusion of normal saline (e.g. 500 ml) prior to commencement of dobutamine may be considered.

Arrhythmias

Arrhythmias during dobutamine infusion reflect the development of ischaemia, the beta-1 receptor stimulation, and perhaps dobutamine-induced reduction in plasma potassium. Arrhythmias are more frequent in patients with previous ventricular arrhythmia or resting left ventricular dysfunction, but are not increased by atropine.

Cessation of infusion due to arrhythmia must be individualised. Isolated ectopic beats are common and do not generally require cessation. Infusion should be stopped and other treatment considered if arrhythmia is sustained, severe or symptomatic.

Termination of infusion may be sufficient to end arrhythmias. Intravenous beta-blockers such as esmolol may also be required, particularly if the arrhythmia is prolonged, there is delayed return to baseline heart rate after dobutamine cessation, or there is evidence of extensive ischaemia.

Reversal of Effects

The effects of dobutamine itself are reversible soon after cessation of infusion. However the effects of stress-induced ischaemia or arrhythmias may persist. Intravenous beta-blockers should be available, such as metoprolol or atenolol or preferably, the short acting beta-blocker esmolol. Esmolol is given as 0.5 mg/kg over 1 minute to reverse the effects of dobutamine. This group of patients may have received dobutamine rather than dipyridamole due to a history of asthma; hence beta-blockers, if required, may need to be administered with caution. Phentolamine injection should also be available for the treatment of dobutamine extravasation.

Specific contraindications

These are similar to contraindications to exercise stress, with particular emphasis on unstable angina, severe hypertension or uncontrolled arrhythmia. Prior adverse reaction to dobutamine should also be noted.

Drug interactions

Background oral beta adrenergic blocker therapy will attenuate the response to dobutamine. See above re cessation of beta adrenergic blockers for stress testing.

Atropine

Rationale for Use

Atropine is an anticholinergic agent frequently used in conjunction with dobutamine to further increase heart rate and therefore increase myocardial oxygen demand resulting in ischaemia. Atropine is more frequently required in patients receiving beta-blockers or with a low resting heart rate. Atropine increases the sensitivity of the dobutamine stress imaging test to detect coronary artery disease, without loss of specificity. It can also be used safely as an adjunct to exercise testing in patients with chronotropic incompetence.

Mechanism of Action

Atropine is an anticholinergic drug which exerts a vagolytic effect on the cardiac conduction system, particularly on the sinoatrial and to a lesser degree the atrioventricular node. This leads to an increase in heart rate.

Duration of Action

The increase in heart rate is observed usually within one minute of injection. Effects on heart rate can persist for a number of minutes and are dose-related.

Administration

Atropine is given by intravenous bolus in 0.3 - 0.6 mg aliquots, given at 1 minute intervals until the target heart rate is reached or to a maximal dose of 1.2 mg.

Adverse Effects

Adverse reactions to atropine include urinary retention, xerostomia, cycloplegia, mydriasis, dry skin, flushing, constipation, nausea and central nervous system disturbance.

Reversal of Effects

Specific reversal is not usually required for cardiac effects as the action is observed to dissipate in the minutes following administration. Urinary retention and cycloplegia require consideration of specific management. In 4 series of 5,717 patients, neurologic manifestations of atropine poisoning developed in 5 patients (0.09%), manifested by stupor and hallucinations, with no permanent sequelae. Management includes supportive measures and consideration of physostigmine.

Contraindications

Narrow angle glaucoma
Obstructive uropathy including bladder neck obstruction from prostatic hypertrophy
Obstructive gastrointestinal disease or paralytic ileus
Atrial fibrillation with uncontrolled ventricular rate
Prior adverse reaction to administration

Due to a risk of hyperpyrexia, atropine should be avoided during a high ambient temperature. Atropine should also be used with caution in patients with chronic pulmonary disease, due to possible reduction in bronchial secretions.

Drug Interactions

The anticholinergic activity of atropine may be increased by other anticholinergic medications, including antihistamines, butyrophenones, phenothiazines and tricyclic antidepressants.

Combined Stresses

Combining vasodilator stress with exercise or combining multiple pharmacologic agents have both been employed in efforts to increase the diagnostic performance of pharmacologic stress imaging techniques.

Vasodilator Stress plus Exercise

Unlike exercise, vasodilators indiscriminately increase blood flow in all vascular beds. The relative increase in hepatic/splanchnic flow is an undesirable consequence for perfusion imaging, affecting evaluation of the inferior wall of the left ventricle for perfusion defects. The addition of a short (up to six minutes) exercise test (treadmill or bicycle) has been used immediately following completion of dipyridamole or during adenosine infusion. This can improve image quality by decreasing splanchnic relative to cardiac blood flow. Tracer injection during the physiologic action of both stresses is required. For this reason, care should be taken to complete exercise testing within the expected period of drug-induced hyperaemic flow.

Multiple Pharmacologic Stresses

Dobutamine/atropine

As detailed above, atropine stress can be routinely used if required in conjunction with dobutamine stress to achieve a diagnostic heart rate response. Atropine can be administered early at the 20 mcg/kg/min stage of the dobutamine protocol if the heart rate is less than 100/minute. This can shorten the test duration, with a similar safety profile and accuracy of the test. This technique has not, as yet, been studied as extensively as the standard protocol of using atropine at peak dobutamine dose.

Atropine can also be combined with the vasodilators although information on the diagnostic efficacy of this technique is less abundant than for the dobutamine/atropine combination.

Dobutamine/Vasodilator Stress

Low dose dobutamine combined with dipyridamole stress has been reported in the assessment of myocardial viability but only in preliminary studies.

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