DIABETES MELLITUS

STANDARD ORAL GLUCOSE TOLERANCE TEST (OGTT)

INDICATIONS

Suspected diabetes mellitus or screening for gestational diabetes mellitus

CONTRAINDICATIONS

None

PRECAUTIONS

Nausea and occasionally vomiting may occur

OGTT not required if diagnosis of diabetes mellitus unequivocal clinically and on fasting or random samples

PREPARATION

Ensure adequate dietary carbohydrate (250g/day) for at least 3 days before the test

Overnight fast.

PROCEDURE

- Insert cannula and take a baseline blood glucose at time 0.
- Oral glucose load (75 g anhydrous glucose in 250–350ml water, or alternatively, Lucozade 394ml (73kcal/100ml formulation) or 410 mls (70Kcal/100ml formulation)
- Repeat blood samples at 60 and 120 min after glucose load.

INTERPRETATION

Plasma Glucose (mmol/l)	Fasting	2 hrs after glucose load
Diabetes mellitus	≥7.0	≥11.1
Impaired glucose tolerance		>7.8 – 11.0
Impaired fasting glucose	>6.1 – 7.0	
Normal	≤6.1	≤7.8

For DM either criterion, on 2 samples or on one sample in association with symptoms of diabetes mellitus. [WHO criteria 2000]

SENSITIVITY AND SPECIFICITY

Acute illness (e.g. myocardial infarction) and drugs may affect glucose tolerance.

REFERENCES

Diabetes Care, 21 S1, 5-19 (1998).

AUTONOMIC FUNCTION TESTS

INDICATIONS

Suspected diabetic autonomic neuropathy.

Suspected autonomic failure from other causes.

CONTRAINDICATIONS

Patients with proliferative retinopathy should not perform the Valsalva manoeuvre because of the risk of retinal haemorrhage.

PRECAUTIONS

Tests uninterpretable in patients with atrial fibrillation, except postural hypotension and handgrip tests).

SIDE EFFECTS

None

PREPARATION

Ensure appropriate equipment available including: sphygmomanometer, anaeroid manometer (or can use sphygmomanometer plus empty syringe without plunger as mouthpiece), ECG machine capable of rhythm strip recording, handgrip dynamometer

PROCEDURE

a) Tests of parasympathetic damage

1. Heart rate response to the Valsalva manoeuvre

Patient sitting; start ECG machine (limb leads only, use lead II) and record continuously through test. Patient blows via mouthpiece into manometer / sphygmomanometer and maintains pressure at 40mmHg for 15 seconds, then relaxing for 60 seconds, over 3 cycles

Measure shortest R-R interval during manoeuvre and longest after

Valsalva ratio = longest after/shortest during (mean of the 3 readings)

2. Heart rate variation during deep breathing

Patient sitting; start ECG machine. Ask patient to breathe quietly at a rate of six breaths over one minute (5 seconds in and 5 seconds out). Mark ECG at start of each inspiration and expiration.

Measure maximum and minimum R–R interval for each cycle and convert to beats/min.

Result is mean difference (max – min) for heart rate during deep breathing.

3. Heart rate response to standing

Start ECG recording with patient lying down. Ask the patient to stand unaided. The point of starting to stand should be marked on the ECG. Continue recording ECG for 1 minute.

Measure shortest R–R interval around the 15th beat after standing and the longest around the 30th beat.

Calculate longest/shortest = 30:15 ratio.

b) Tests of sympathetic damage

4. Blood pressure response to standing

Start with patient lying down.

Measure blood pressure lying and then 2 minutes after standing

Record the postural difference between lying and standing systolic pressure

5. Blood –pressure response to sustained handgrip

The maximum voluntary contraction is determined using a handgrip dynamometer. Handgrip is maintained to 30% of maximum for as long as possible up to 5 minutes. Blood pressure is measured three times before and at 1 minute intervals during handgrip. Calculate the difference between highest diastolic pressure during handgrip and mean of 3 diastolic readings before handgrip.

INTERPRETATION

TESTS	Normal	Borderline	Abnormal
Valsalva ratio	≥1.21	1.11-1.20	≤1.10
(max–min) HR	>15	11-14	<10
(30:15 ratio)	>1.04	1.01-1.03	≤1.00
fall in BP	≤10	11-29	≥30
Diastolic change handgrip	≥16	11-15	≤10

Abnormalities in at least two parasympathetic tests suggests mild / early damage

Abnormalities in two or more of the parasympathetic tests plus the sympathetic tests indicate significant autonomic damage

SENSITIVITY AND SPECIFICITY

Interpret with caution in patients who are poorly co-operative and in the elderly.

REFERENCE

Clarke B.F. and Ewing D.J., BMJ 285, 918-920 (1982).

INSULINOMAS

i) SUSPICION OF A HYPOGLYCAEMIC DISORDER

Documentation of Whipple's triad (Symptoms of neuroglycopaenia, occurring at the time of low blood glucose which resolve when the glucose is corrected) is the cornerstone, although may not always be possible to confirm all of these completely prior to investigation.

Depending on presenting symptoms also consider:

- Close review of drug history for medications that may provoke hypoglycaemia
- Neurological investigations (EEG and CT brain for possible temporal lobe epilepsy)
- Cardiac investigations (ECG, Holter monitor for possible arrhythmia)

ii) EXCLUSION OF OTHER CAUSES OF HYPOGLYCAEMIA

Check liver and renal function, thyroid function tests, 9am cortisol
Corroborative tests may include HbA1c (not diagnostic)

iii) PROVOCATION TESTING

Proceed to provocation testing, unless serendipitous measurement of glucose, insulin and C-peptide has been possible during a spontaneous episode.

REFERENCE

Cryer PE et al J Clin Endocrinol Metab. 2009 Mar;94(3):709-28.

Provocation tests for hypoglycaemia

1) PROLONGED MIXED-MEAL TEST

INDICATIONS

Diagnosis of insulinoma when prolonged fast negative.

Current guidelines do not recommend prolonged glucose tolerance test

CONTRAINDICATIONS

None

PRECAUTIONS

None

PREPARATION

Ensure adequate dietery carbohydrate (250g/day) for at least 3 days before the test

Overnight fast. Perform before (and not immediately after) prolonged supervised fast

PROCEDURE

Insert cannula and take a baseline glucose at time 0.

Give mixed meal* or food suspected of inducing hypoglycaemia.

Repeat blood samples at +15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270 and 300 min.

Take blood for glucose, insulin and C-peptide but do not process insulin and C-peptide unless hypoglycaemia confirmed biochemically.

INTERPRETATION

Blood glucose <2.2mmol/L during the test suggests reactive hypoglycaemia.

SENSITIVITY AND SPECIFICITY

A proportion of patients with insulinoma will show a positive test (approx 8%).

Suggested mixed meal:
30 g cornflakes
250ml semi-skimmed milk
4.5g sachet sugar
170ml unsweetened orange juice
40g (medium) slice white bread
10g portion butter
50g piece cheddar cheese
100g low fat fruit yoghurt

This will provide:
31.1g Protein / 124.4 kcal / 16%
31.1g Fat / 297.9 kcal / 38%
95.6g CHO / 358.5kcal / 46%
For a 75kg person this would be 10.4kcal/kg & 1.3g/kg CHO

2) PROLONGED SUPERVISED FAST

INDICATION

Demonstration of fasting hypoglycaemia

Biochemical diagnosis of insulinoma if not shown spontaneously or after an overnight fast.

CONTRAINDICATIONS

None specific

PRECAUTIONS

Admit to perform test under close supervision with glucose (p.o./i.v.) available.

Ensure protocol understood by the patient and nursing staff

Contact lab to ensure availability of glucose results urgently

PREPARATION

Discontinue diazoxide for a week before start of fast.

PROCEDURE

- Cannulate patient. Test should take place on open ward for adequate supervision.
- Water and non-caloric beverages allowed. Ensure no other food / drinks available. Patient should be active during waking hours.
- Measure blood glucose every 4-6 hours and whenever the patient has symptoms suggestive of hypoglycaemia. If glucose < 3.0, test blood glucose every 2 hours.
- If blood glucoses are ≤2.2 mmol/l or symptoms are convincing:
    - Take blood for glucose, insulin and C-peptide
    - Take blood for sulphonylurea screen
    - Send glucose for urgent analysis, separate and freeze remaining samples within 30 mins
    - Reverse hypoglycaemia only when the lab confirms hypoglycaemia, unless the patient becomes unconscious or fits.
- If patient asymptomatic at 72 hours, complete the test with 10-20 mins exercise, e.g. walking up and down the stairs under supervision
- Take final samples for glucose, insulin and C-peptide, sulphonylurea screen. Dipstick urine for ketones or measure plasma beta-hydroxybutyrate.

INTERPRETATION

- True hypoglycaemia must be demonstrated (glucose ≤2-2.2 mmol/l), in order to interpret insulin results or consider insulinoma.
- If hypoglycaemia with raised insulin but low C peptide, consider self administration of insulin.
- If hypoglycaemia with raised insulin, and raised C-peptide, ensure sulphonylurea screen is negative
- In the presence of hypoglycaemia:
    - Insulin >3 mU/l and C peptide >200 pmol/l consistent with insulinoma (also review ratio of C-peptide to insulin).
    - Insulin >3-6 mU/l (25-50 pmol/l); C peptide 100-300 pmol/l equivocal result
    - Insulin <3 mU/l (<25 pmol/l); C peptide <75 pmol/l is appropriate; seek alternative cause of hypoglycaemia
- Ketones should be suppressed with insulinoma even though patient is fasting because of the excess insulin (measure urinary ketones or plasma beta-hydroxybutyrate).

SENSITIVITY AND SPECIFICITY

By 24 hrs, 66% insulinomas develop hypoglycaemia and by 48 hrs, >95% insulinomas can be diagnosed. After 72 hrs fast plus exercise, if no hypoglycaemia, insulinoma is very unlikely.

REFERENCE

Cryer PE et al J Clin Endocrinol Metab. 2009 Mar;94(3):709-28.

ADDITIONAL INVESTIGATION

In the presence of a biochemical diagnosis of insulinoma the next step is localisation.

- In addition to localizing information, seek corroborative tumour markers eg chromogranin A and B.
- Also seek evidence of coexisting endocrine disorders with serum calcium and anterior pituitary hormones to identify MEN-1

LOCALISATION OF INSULINOMAS

Available methods:

Pancreatic imaging has variable sensitivity and specificity – insulinomas may be very small and below the limit of detection of the scan and incidental pancreatic nodules are common. Several modalities are often required to ensure corroboration.

- CT scan performed using pancreatic protocol or MRI will demonstrate structural abnormalities of the pancreas. Both may be required; discuss in the radiology meeting. Diffusion weighted MRI images may be particularly sensitive.
- Endoscopic ultrasound is helpful for insulinomas especially in the head of the pancreas. Arrange by faxed referral to the gastroenterology team and confirmation of date with endoscopy reception. **Please note : preparation for endoscopic ultrasound (EUS)** requires a prior fast but insulinoma patients are at risk of hypoglycaemia and will therefore require admission for an iv dextrose infusion from midnight.
- Somatostatin receptor imaging (*Octreoscan*) may be useful for corroboration of structural findings but test has moderate sensitivity (positive in approx 50% of insulinomas)
- Selective arterial injection (calcium stimulation test) provides functional as well as some (limited) structural information.

SELECTIVE ARTERIAL INJECTION / Calcium Stimulation test

INDICATION

Localisation of insulinoma

CONTRAINDICATIONS

Allergy to contrast dye.

Ischaemic Heart Disease

Orthopnoea

Severe bleeding tendency (if patient on aspirin/clopidogrel, discuss with radiologist)

PRECAUTIONS

Stop diazoxide 7 days before procedure [elimination half-life variable 21-36 hours]

Flushing and nausea may follow calcium injection.

Monitor BMs and maintain glucose at 3 - 5 mmol/l with dextrose infusion if necessary.

Risks of angiography itself: bleeding from sheath sites, thrombosis/dissection of femoral artery and visceral arteries, dye allergy

PREPARATION

Radiologist should consent patient

Blood for FBC, U+Es, clotting, and G+S should be taken the day prior to the procedure.

Prior to the test patient should fast for at least 4 hours. Have 5% dextrose drip available; if hypoglycaemic, administer at rate to maintain blood glucose at about 3-5 mmol/l (not more).

Advance preparation and careful labelling of series of tubes for each run (4 plus 2 spare runs).

Calculation of calcium to be injected:

Each calcium injection should be 0.003125 mmol/kg body weight, in 5ml volume

Calculate this as follows:
Number of mmol needed per aliquot is 0.003125 x weight in kg.

For the number of mmol needed in 100ml saline this would be the above figure x (100/5)

Calculate the volume of 10% calcium gluconate containing this number of mmol; knowing that 10% calcium gluconate contains 225mmols per 1000ml.

Therefore number of mls of calcium gluconate needed is:
(Body weight x 0.003125) x (100/5) x (1000/225).

i.e. Body weight (in kg) x 0.2778 = mls of calcium gluconate

Remove this number of mls from a 100ml bag of saline and replace with equivalent volume of calcium gluconate

Draw up and inject in 5ml aliquots

PROCEDURE

1. A catheter is placed in the right hepatic vein prior to routine highly selective visceral angiography.
2. Following angiography each artery (usually proximal gastroduodenal, proximal splenic, hepatic and superior mesenteric) is recatheterised in turn, preferably starting with the vessels least likely to be supplying the tumour. Occassionally the dorsal pancreatic artery is also catheterised.
3. Take two baselines at T = -120 and 0 secs. Check BM on the samples and note result.
4. At T = 0 calcium gluconate is rapidly injected as a bolus into the artery
5. Blood is sampled at T = 30, 60, 90, 120 and 180 secs (give a 10 sec countdown before each sample). Check BM on the 180 second sample.
6. Samples for insulin and C-peptide should be separated within 30 minutes. Store on ice if procedure very prolonged.

INTERPRETATION

The criterion for localisation is a two-fold rise in insulin in the 30 or 60 sec hepatic vein samples following injection into the relevant arterial territory

REFERENCES

Doppman J.L. et al., Radiology 178, 237-241 (1991), Fedorak I.J. et al., Surgery 113, 242-249 (1993)

Cryer PE et al J Clin Endocrinol Metab. 2009 Mar;94(3):709-28.

MEDICAL MANAGEMENT OF INSULINOMAS

Definitive therapy is surgical.

Where this is contraindicated, or until it can be arranged,

ALTERNATIVES INCLUDE:

1. Dietitian review. Multiple, regular, small meals usually help.
2. Guar gum 5g tds also helps by slowing gastric absorption.
3. Diazoxide 50–200 mg tds, but beware of hypokalaemia and severe oedema, and in the longer-tern hirsuties
4. NG feeding can be considered.
5. Steroids can help for a short period.
6. Octreotide can be helpful but beware hypoglycaemia if glucagon levels are suppressed.
7. Calcium channel antagonists may be useful for nesidioblastosis eg verapamil.
8. Phenytoin
9. RAD001 (everolimus, Novartis) useful in published literature (not licensed for this use at present, but may be available for compassionate use)

GASTRINOMAS

GASTRIC ACID SECRETION

Used in the diagnosis of Zollinger-Ellison syndrome.
Formal gastric acid output studies are rarely needed now as an endoscopy can give evidence of acid hypersecretion (multiple ulceration) and usually can distinguish achlorhydria.
Acid output studies may be technically difficult to arrange and perform.
An alternative is to take a single gastric pH measurement using a wide bore nasogastric tube and pH measurement.
A basal gastric pH of >2 virtually excludes a gastrinoma.

Consider the syndrome if:

1) Raised gastrin (>40 pmol/l) in the absence of other causes (e.g. H2 antagonists, PPIs, pernicious anaemia, other causes of achlorhydria, renal failure).
2) Associated upper gastrointestinal disease, i.e. peptic ulcer disease with poor response to treatment; multiple duodenal or jejunal ulcers; peptic ulcer disease with unexplained diarrhoea; fulminant peptic ulcer disease (perforation, haemorrhage, oesophagitis and stricture); ulcer in upper part of ligament of Treitz.

INTERPRETATION

Hypergastrinaemia and raised gastric acid are also found with:

1. gastric outlet obstruction: resolves with NG decompression
2. massive small bowel resection: resolves a few months post op
3. antral G cell hyperplasia: excess cells on histochemistry

LOCALIZATION OF GASTRINOMAS

Procedure etc as per section on localisation of insulinomas.

CARCINOID AND OTHER NEUROENDOCRINE TUMOURS

INVESTIGATIONS FOR 'CARCINOID SYNDROME'

i) Tumour products / markers:

- Urine: 24-hour urine collection for 5HIAA x 2
- Serum: chromogranin A and B, CEA. Some evidence that β-hCG may be a useful marker.

FOODS TO AVOID DURING 24 HOUR URINE COLLECTION FOR 5-HIAA:
Avocados, bananas, plums, walnuts, pineapples, tomatoes, aubergines, pecan nuts, cough medicine.

ii) Basal investigations including FBC, UandE, LFT's, Clotting.

ii) Echocardiogram for cardiac fibrosis. Pro-BNP may be a useful predictor of cardiac involvement although not routinely offered at present.

iv)Pulmonary function tests for bronchoconstriction if clinically indicated

v) Imaging: CT scanning with arterial phase imaging for hypervascular liver metastases, MRI abdomen may be better at detecting liver metastases.

vi) Nuclear Medicine
MIBG scan useful for predicting utility of MIBG therapy.
Octreotide scan may help predict symptomatic response to somatostatin analogues and suggest future potential utility of radiolabelled somatostatin analogues. Most patients will probably need octreotide scintiscanning.

vii) Performance status is an important predictor of prognosis – various scoring systems available

Performance Status Scale – ECOG score

0 Asymptomatic (Fully active, able to carry on all predisease activities without restriction)
1 Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2 Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3 Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4 Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
5 Death

SOMATOSTATIN ANALOGUES FOR NEUROENDOCRINE TUMOURS

Many neuroendocrine tumours express somatostatin receptors, particularly subtypes 2 and 5. Thus somatostatin analogues may be helpful in ameliorating symptoms caused by functional hormone secretion from the tumours.

Available analogues include:

Octreotide (short acting, subcutaneous injection. Start with an injection of 50mcg as a test dose, titrate up according to symptoms. May require multiple daily injections. Can be used to 'top-up' long acting preparations)

Sandostatin LAR (long-acting octreotide preparation. Given as deep im injection 20-30mg every approx 4 weeks therefore unsuitable for patients taking warfarin).

Lanreotide autogel (SC injection every 4 weeks, usual dose 60-120mg per injection. Post-marketing surveillance study ongoing in which patients can elect to self-inject).

Some evidence that for at least some subgroups of neuroendocrine tumours, these drugs have an effect on reducing rate of tumour growth as well as clear effects on function.

HEPATIC EMBOLISATION OF METASTASES

(Based on the "Hammersmith" protocol)

The liver has a dual blood supply (hepatic artery and portal vein) so that interruption of hepatic arterial supply by its embolisation using foreign substances (e.g. polyvinyl alcohol) in the presence of a patent portal circulation (necessary to sustain liver function) can be undertaken to devascularise liver metastases.

INDICATIONS

- Palliation of clinical consequences of hormone production from hepatic secondaries in the carcinoid syndrome and other neuroendocrine tumours. The diagnosis should be fully established.
- More controversially: reduction of tumour load in these patients to improve the well being of the patient or to reduce local symptoms (e.g. "dragging" abdominal pain from hepatomegaly). However, recent data suggest that such therapy may lead to increased survival.

CONTRAINDICATIONS

Prolonged prothrombin time

Non-patent portal circulation

Obvious end-stage illness

Ischaemic heart disease

Contrast allergy

PRECAUTIONS

Potential side-effects include:

- Arterial thrombosis (e.g. femoral artery).
- Bleeding from sites of sheath insertion.
- Malaise, mild hypotension and fever due to the release of tumour necrosis factor and other vasoactive compounds from necrotic tissue. This can last for weeks after the procedure.
- Occasionally, life threatening hypovolaemia with renal failure due to severe vasodilatation. This is now rare when octreotide is used, but patients must be well hydrated pre- and immediately post-embolisation.
- Rarely, infarction of other intra-abdominal organs including the gallbladder.
- Rarely, infection introduced during procedure and or abscesses in the liver, which can develop late.
- Rarely, 'tumour lysis syndrome' (which is why allopurinol has been added to protocol).

PREPARATION

1 week before procedure:

- Dual-phase contrast CT abdomen to establish baseline for size and location of metastases.
- *Optional* Doppler USS liver to establish portal vein patency (this may be established by the radiologist immediately before embolisation).
- Take blood for FBC, U+Es, clotting, G+S.
- CXR, ECG.
- Echocardiogram if carcinoid and none previously performed.

Day before:

- May need to put in central venous catheter and urinary catheter (low threshold).
- Insert three large cannulae, if not using central venous catheter.
- Document foot pulses.
- No evidence of infection.
- Informed consent.
- Premed (discuss with radiologist).
- Discuss with anaesthetic SR on call regarding possible need for ITU bed.
- Start 1L 0.9% saline with 20 mmol KCl from midnight before procedure.
- Write up protocol medication (see below)
- CLOSE LIAISON WITH HEPATOBILIARY TEAM AT RLH TO ENSURE ALL MEDICATIONS ETC ARE AVAILABLE, PRESCRIBED AND GIVEN.

PROCEDURE

Start on admission:

- Allopurinol 300 mg p.o. od for 10 days.
- Cyproheptadine 4 mg p.o. tds (histamine blocker – in *carcinoids*) for 72 hrs post procedure.
- Nicotinamide no longer used as it causes extreme flushing in carcinoids. It can be used in lower doses chronically to avoid Pellagra.

To start on morning of procedure and continue for 48 hrs:

- Octreotide: 1600 mcg in 48 ml 0.9% saline, i.v. at 6 ml/hr (i.e. 8 hrs). Write up 6 syringes.
- Trasylol (aprotinin): 50 ml <u>neat</u> (10,000 U/ml) i.v. at 5 ml/hr (i.e. 10 hrs). Write up 5 syringes.

One hour before procedure:

- Methylprednisolone 1g i.v.
- Premedication (to be discussed).

Antibiotic cover:

Pre-procedure

- Amoxycillin 1g i.v. (or Teicholplanin 400 mg 12 hourly if penicillin allergic).
- Metronidazole 500mg i.v.
- Gentamicin 120mg i.v.

Post-procedure

2 further doses of

- Amoxycillin 1g i.v. 8 hourly
- Metronidazole 500mg i.v. 8 hourly

Have available:

- Hydralazine i.v. for hypertension (alternatively nitroprusside, labetalol).
- Colloids for hypotension.
- Methylprednisolone.

POST-EMBOLISATION:

Usual post angiogram observations (i.e. foot temperature, peripheral pulses, Tº, BP and HR).

Careful attention to fluid balance is needed.

Daily biochemistry including GGT, CRP, and haematology for at least 3 days.

Monitor specific tests, e.g. urinary 5-HIAA in carcinoid syndrome or gut peptides, every other day.

Expect pyrexia and malaise for up to 10 days but perform blood cultures daily until pyrexia subsides.

If abdominal symptoms persist, arrange appropriate investigations (erect and supine X-rays, U/S abdomen) and ask for a surgical opinion.

POST-EMBOLISATION, PATIENTS MAY BE IN TRANSIT FROM RLH to SBH. BE AWARE that they need close observation and monitoring,

OUTCOMES

In approximately 60%-80% of patients who have symptoms from secreting hepatic secondaries, there will be an improvement with embolisation. Revascularisation will occur with a recurrence of symptoms after weeks, months or years, but the procedure can be successfully repeated.

REFERENCES

Allison D.M., Br. J. Hosp. Med. 20, 707-715 (1978).

Adjani J.A. et al., Ann. Intern. Med. 108(3), 340-4 (1988).

CHEMOTHERAPY FOR NEUROENDOCRINE TUMOURS

Coordinate with oncology: Dr Plowman's team.

INDICATIONS

Patients with established neuroendocrine tumour, to reduce tumour bulk and improve symptoms

INVESTIGATIONS

(to monitor renal, hepatic and bone marrow function, and response to treatment)

- 24-hr urine for creatinine clearance: chemotherapy contraindicated if <60 ml/min.
- Urinalysis twice daily during treatment and abandon if persistent proteinuria.
- FBC and biochemical profile on alternate days.
- Gut hormone screen and urinary 5HIAA before and after treatment.
- CT scanning and ultrasound where appropriate.

CURRENT TREATMENT PROTOCOLS

Lomustine with 5FU, or
Lomustine with capecitabine
For well-differentiated tumours.

Platinum-based regimes eg: cisplatin, doxorubicin, etoposide
For poorly differentiated tumours.

Second-line therapy with temozolomide for well-diferntiated tumours, especially from fore-gut, progressing after conventional chemotherapy above.

Newer anti-tumour therapies eg sunitinib, everolimus etc occasionally tried.

Some centres use Interferon therapy but only poor evidence that this adds to somatostatin analogue therapy and often poorly-tolerated; if used, consider weekly pegylated inerteferon (expensive).

REFERENCE

Oberg et al., Acta Oncol. 28, 425 (1989).

RADIONUCLIDE THERAPY FOR NEUROENDOCRINE TUMOURS

1) MIBG THERAPY

INDICATION

Treatment of inoperable or metastatic neuroendocrine tumours which are MIBG-avid on MIBG scanning, in patients with good performance status

CONTRAINDICATIONS

Pregnancy or its possibility, allergy to iodine.
Caution in any patient with any drug allergies.
Inability to comply with radiation protection instructions.
Urinary or faecal incontinence

PRECAUTIONS

May be unsuitable for patients with myelosuppression, bone marrow metastases, renal impairment, extensive hepatic involvement, poor performance status.
Short-term side effects may include nausea and vomiting, dry mouth
Medium-term may cause (usually transient) myelosuppression, renal impairment, deranged liver function.
Ensure maximum allowable radiation dose has not been reached.

PREPARATION

Planned admission to 'hot room' and close liaison with nuclear medicine department.
Thyroid uptake should be blocked by **potassium iodide 60 mg bd** for 48 hours beforehand and for 5 days afterwards.

PROCEDURE

MIBG is administered in the nuclear medicine department, with a dose decided at a prior MDT or using prior dosimetry. Patient to remain in the 'hot room' until deemed to have cleared sufficient radioactivity to comply with legal regulations. No blood or urine testing possible in the post-therapy period. 'Tail-end' scan performed prior to discharge. May be repeated at 6-monthly intervals until disease progression or maximum dose achieved.

REFERENCES

Sisson J.C. et al., New Engl J Med 1981; 305: 12-17.

Shapiro et al., Cardiology 1985; 72: suppl. 1, 137-142.

2) RADIOLABELLED SOMATOSTATIN ANALOGUE THERAPY

INDICATION

Treatment of inoperable or metastatic neuroendocrine tumours which are octreotide avid on octreoscan, in patients with good performance status

CONTRAINDICATIONS AND PRECAUTIONS

Similar to MIBG therapy

Therapy not given at Barts Hospital.

For ^{90}-Y-DOTATOC treatment: Referral to Dr Val Lewington, Royal Marsden Hospital, Sutton, Surrey