

Iohexol GFR measurement – for use in potential Living Kidney Donors

The UK Guidelines for Living Donor Kidney Transplantation (1) recommend donor glomerular filtration rate (GFR) should be estimated from serum creatinine initially, and then assessed by a reference measured method (mGFR) such as clearance of ⁵¹Cr-EDTA, ¹²⁵I-iothalamate or Iohexol. ⁵¹Cr-EDTA is the most widely available reference test but ⁵¹Cr-EDTA will not be available for clinical use in the UK beyond March 2019.

Characteristics of Iohexol

Iohexol is a non-ionic contrast medium, used routinely in the NHS for computed tomography (CT), catheter-based angiography and interventions. It has low extra-renal excretion, low protein binding (2-5) and is neither secreted nor reabsorbed by the kidney. Extra-renal clearance of Iohexol is low and comparable to that for ⁵¹Cr-EDTA: extra-renal clearance of Iohexol is reported as 0-6 ml/min/1.73m² (2, 5, 6) compared to 2-4 ml/min/1.73m² for ⁵¹Cr-EDTA (7, 8). Iohexol carries low risk of toxicity (9) and doses of 10ml of 300mg Iodine/ml preparations (e.g. 10ml of Omnipaque 300™) have not been shown to be nephrotoxic (10). Iohexol is available as Omnipaque™ with different preparations reflecting different concentrations of iodine/ml. Omnipaque 300™ (300mg iodine/ml) and Omnipaque 240™ (240mg iodine/ml) are the most commonly used for GFR measurement.

Iohexol is stable in plasma at room temperature, -20°C and -80°C (11) therefore samples can be collected then transferred to a distant laboratory for analysis. Equalis AB, Uppsala, Sweden provides an external quality assurance programme through which all laboratories can compare their results with those of other participating laboratories.

Comparison to other markers

Good correlation between Iohexol estimates and urinary inulin clearance in adults has been demonstrated (12). A systematic review and meta-analysis from 2014 compared plasma Iohexol-clearance and ⁵¹Cr-EDTA-clearance measurements with inulin clearance and found GRADE rated 'moderately strong evidence' that both methods are sufficiently accurate for measuring GFR (13). Excellent agreement has been demonstrated between ⁵¹Cr-EDTA-clearance and Iohexol-clearance estimates (14, 15) (correlation co-efficients 0.92-0.95). Agreement with ⁹⁹Tc-DTPA methods has not been well-demonstrated. Plasma Iohexol clearance measurement is more practicable than urinary clearance methods but plasma clearance methods produce higher measurements than urinary clearances (16). Concordance between the two methods improves if the last plasma Iohexol measurement is performed late.

Variability

For the same individual, measured GFR will vary over time, regardless of method used. Some of this variation is due to physiological parameters including activity and diet (physiological variation). Some of this is due to measurement error (method variation (coefficient of variance)). Intra-individual variation of Iohexol-measured GFR has been reported at between 4.2 and 11.4% (16), which is comparable to the reported intra-individual variation of mGFR independent of the marker used. A standardized protocol (as outlined below) reduces physiological variation.

Analysis

The most validated methods for measuring Iohexol are:

- High performance liquid chromatography with ultraviolet detection (HPLC-UV)
- X-ray fluorescence (XRF)

- Liquid chromatography-tandem mass spectrometry (LC-MS/MS)

HPLC-UV is the most commonly used method in Europe and it is reproducible highly sensitive and specific (9). XRF requires specific instrumentation and appears to be less sensitive than HPLC-UV (14). LC-MS/MS may be more sensitive and specific when compared to HPLC-UV but is more complex and costly (17). Concordance between GFRs measured using HPLC-UV and LC-MS/MS is high (18).

Measurement of plasma clearance

After a bolus intravenous injection, plasma iohexol concentration will decrease. The clearance occurs according to two different exponential curves corresponding to i) distribution in the extracellular volume and ii) renal elimination of iohexol. In a semi-logarithmic plot these phases can be illustrated by two lines, the slopes of which are proportional to the half-life of each phase. To allow calculation of clearance without multiple short interval samples being taken to measure the fast distribution phase, a mathematical correction is required. The most commonly used is that proposed by Bröchner-Mortensen (BM)(19) (see Box 1). This mathematical correction risks an underestimation of high GFR levels (20). The Brochner-Mortensen correction is currently applied to ⁵¹CrEDTA GFR measurements.

Box 1 Plasma iohexol clearance calculations

Slope-intercept GFR (ml/min)

= $k \times \text{iohexol dose } (\mu\text{g}) / C_0 (\mu\text{g/mL})$ where k is the slope of the semilog plot of plasma iohexol concentration versus time (plotted using 3 points, refer above), and C_0 is the calculated iohexol concentration at time zero (intercept).

This value is multiplied by 1.73 and divided by the body surface area (BSA, calculated from the Du Bois equation

$$\text{BSA} = 0.007184 \times \text{height (metres)}^{0.725} \times \text{weight (kg)}^{0.425}$$

The BSA-slope intercept GFR value (mL/min/1.73 m²) is corrected by the BM correction factor

$$= (0.990778 \times \text{GFR}) - (0.001218 \times \text{GFR}^2)$$

providing a reference GFR value (mL/min/1.73 m²)

Sampling protocols

Single-sample and multiple-sample protocols exist for iohexol mGFR (15). The single-sample method is simpler and less expensive but difficulty in estimating the extracellular volume of distribution is a significant source of error compared to the multiple-sample method. Multiple-sample GFR is likely to be more precise than single-sample methods, and any errors resulting from mistiming or mislabelling of samples can be easily identified and excluded, or the process repeated if necessary

(16). For these reasons when measuring GFR in potential living kidney donors, the multiple-sample method is currently recommended (16).

In all approaches the timing of the samples ,and the accurate recording of these times, is crucial. For potential living kidney donors (with eGFR $\geq 45\text{ml/min/1.73m}^2$) we recommend the last sample is taken 4 hours after the iohexol bolus injection (16).

Contraindications

It is not safe for the following people to have this test:

- Pregnant women (absence of safety data)
- People with iodine sensitivity, allergy or anaphylaxis (consider $^{99\text{m}}\text{Tc-DTPA}$ mGFR or alternative eGFR measurements in this rare situation)
- People with a history of a severe allergic reaction to iodinated contrast e.g. when having a CT scan (Severe allergic reactions include difficulty breathing, chest pain, chest tightness, a rash, hives, swelling of the face, itching, dizziness, collapse and loss of consciousness)
- Thyrotoxicosis or awaiting diagnostic thyroid scintigraphy or radio-iodine treatment

Results will not be accurate in:

- People with ascites or generalised oedema
- People with an external drain e.g. an external ventricular drain or chest drain.
- People who have fasted/dehydrated individuals.
- People who have been hyperhydrated e.g. for certain types of chemotherapy
- There is a theoretical risk of QTc prolongation with concurrent use of Amiodarone and Iohexol and increased risk of lactic acidosis in patients on Metformin. An individualised risk-vs-benefit ratio evaluation and informed consent from patients is recommended if the potential living kidney donor is currently on either medication.

Preparing for the test

The following should be avoided from 7pm the night before the test:

- Tobacco (smoking), alcohol, coffee, tea, chocolate
- Meat and meat products
- Eggs, cheese (including cheese spreads), yoghurt, fish (including fish cakes or fish fingers) and baked beans

This means avoid eating meat for dinner the day before the test, and for breakfast on the day of the test.

Medications

Common painkillers e.g. paracetamol, anadin, ibuprofen, should not be taken for 24 hours before the test. All other medications should be taken as routine.

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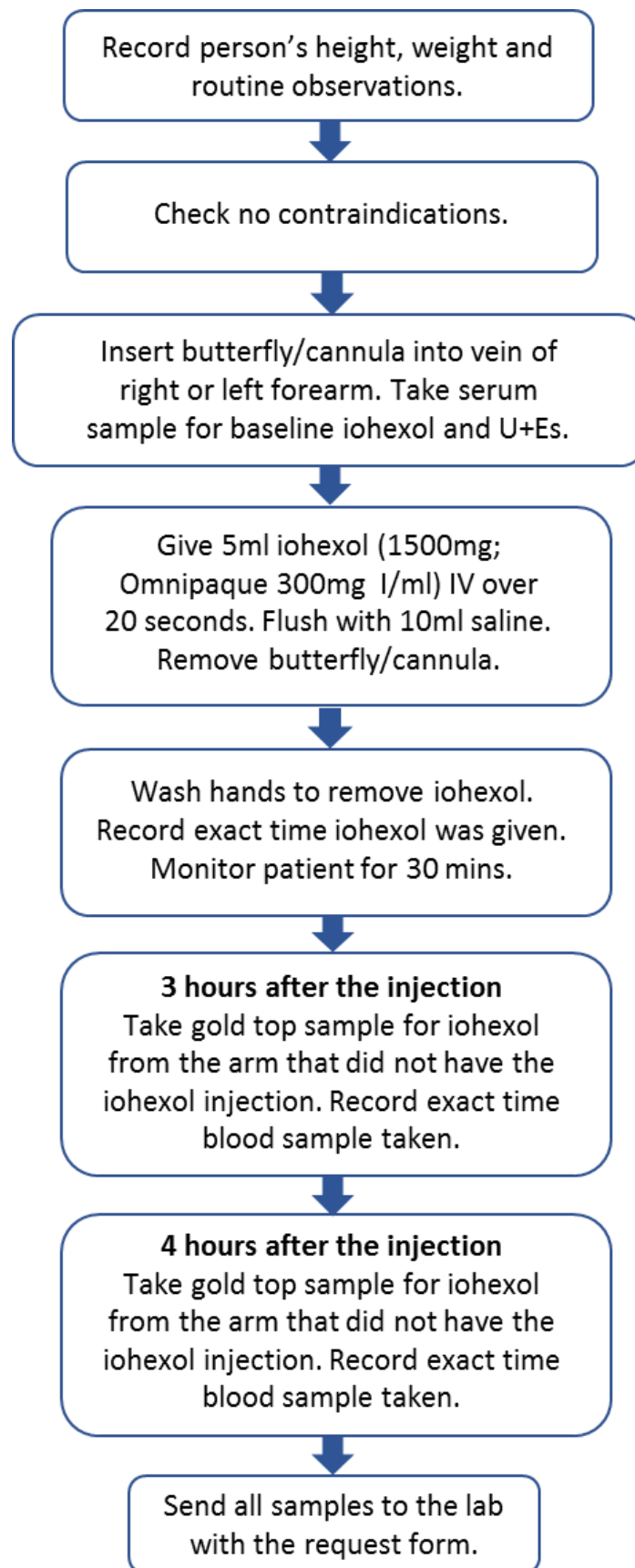
Protocol for the measurement of GFR using iohexol plasma clearance

1. The protocol may be followed by clinical staff who have been trained in this process and have had their competency signed off.
2. Obtain verbal consent.
3. Record weight, height and observations on the iohexol GFR request form which should be sent to the lab.
4. Insert a cannula or butterfly needle into one arm. Obtain a gold top blood sample from the cannula or butterfly needle. This is the baseline (0 min).
5. Contamination of the environment by iohexol occurs through iohexol on hands and iohexol aerosol when removing air from syringe. The preparation of iohexol must be on a different surface to where the blood tubes are kept.
6. Draw up 5ml iohexol (1500mg; Omnipaque 300mg I/ml) and give IV over 20 seconds .Flush the cannula/butterfly that was used for the iohexol administration with 10ml saline, and then remove it.
7. Wash hands to remove iohexol to prevent contamination. Record exact time iohexol was given.
8. Monitor patient for 30 mins. Thereafter they are allowed to leave the outpatient department but must remain in the hospital and avoid strenuous activity.
9. The patient should return to have gold top blood samples taken at 3 and 4 hours after the injection. The blood samples must be taken from the opposite arm to the one into which the iohexol was injected. The samples for iohexol may be taken by 2 single takes at 3 hours and 4 hours.
10. The precise time that the samples are collected must be written on the form. It is very important to accurately record the exact times at which samples are taken, to the nearest minute, using the same clock/watch. These should be gold top samples.
11. Send the request form for iohexol clearance together with the four blood samples to the lab. Samples can be stored or transported at room temperature and will remain stable for up to 9 days.

Adverse effects

Serious adverse effects are very uncommon. Hot flushes, altered taste, abdominal discomfort, nausea and vomiting can occur and rarely local reaction at the site of injection (pain, redness and swelling). The procedure should be undertaken in a facility with access to equipment and expertise with management of severe anaphylactic reaction.

Figure 1: Iohexol measured GFR flow chart



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