CKiD sample response if IRB requires additional information about Iohexol

1) Please provide information on the risks of the low dose iohexol you plan to use in this study.

Our review of the literature suggests that the risks of iohexol in the doses used for GFR measurement in this study are minimal. Iohexol is a non-ionic x-ray contrast medium of low osmolality, extensively used in clinical radiology and considered essentially free from side effects (Almen, Acta Radiol 366; 9-19, 1983, Schrott, Fortschr Med 104; 153-156, 1986, Albrechtsson , Acta Radiol Diagnosis 26: 615-618, 1985). It has been used as a method for the determination of GFR in clinical work and in clinical research since the mid 1980's in Sweden, and has largely replaced Cr-EDTA clearance for the measurement of GFR. A paper by Nilsson-Ehle in the electronic Journal of International Federation of Clinical Chemistry and Laboratory Medicine (Iohexol clearance for the determination of glomerular filtration rate: 15 years´ experience in clinical practice, Nilsson-Ehle P, eJIFCC vol 13 no 2: http://www.ifcc.org/ejifcc/vol13no2/1301200105.htm) summarizes the experience with approximately 8000 iohexol GFR determinations using a dose of 5 ml of iohexol (OMNIPAQUE, Nycomed GE Healthcare, 300 mg I(iodide)/L) intravenously. Using this protocol during 8000 investigations, the authors reported no complications except for 2 patients who reported transient malaise and vomiting between 1 and 3 hours after injection of the iohexol. It was uncertain whether these were indeed caused by the iohexol.

In attempting to more clearly assess the risk of iohexol in the pediatric population with chronic kidney disease, we contacted Dr. Nilsson-Ehle directly and asked about his experience with iohexol in children. His response to our inquiry is pasted below:

"We routinely perform iohexol clearance measurements in children, also with kidney function impairment. We have not encountered any side effects."

We also performed an additional literature search on iohexol GFR measurement in pediatrics. A paper published in Pediatr Nephrol (2002) 17:847-851 by Hjorth et al described the use of iohexol to measure GFR in 69 children with hematologic or oncologic problems (734 iohexol GFR measures). They reported no adverse events.

Few published studies report on the use of iohexol to measure GFR in children with chronic renal failure. One study, (Stake et al, Scand J Clin Lab Invest 1991; 51:729-734) described the use of iohexol GFR measurement in 11 children, average age 9 +/- 1 year, body weight 27 +/- 3 kg with creatinine clearances ranging from 4.1- 28.4 ml/min/1.73 m^2. In this group, the plasma creatinine was not significantly increased 24 hours after the injection of iohexol in the patients examined. The authors suggested that as low a dose of iohexol as possible should be used, and recommended an iohexol dose corresponding to 175 mg I/kg for a patient weighing 10 kg, and a dose corresponding to 100 mg I /kg for a 50 kg patient. This corresponds to 5 ml of Omnipaque 300 in a 10 kg child, and 14 ml in a 50 kg child. Our proposed dose of 5 ml in all children is below this recommended level.

Three studies of iohexol for excretory urography using iohexol in children with urologic disease have been published (Bolz et al, Acta Radiologica Diagnosis 1984: 25:155-158). No serious adverse reactions were noted; 2 children complained of mild heat sensation, and 3 children experienced brief nausea with small amounts of emesis. Accidental extravasation of iohexol in 11 children produced no visible discomfort or local inflammation. No children demonstrated any adverse changes in serum blood urea nitrogen concentrations and creatinine levels. Our recommended dose is below the dose used in these studies: Eyeset al, Clinical Radiology 1987; 38: 403-405, Magill et al, Radiology 1986; 161:625-630). Each utilized a dose of iohexol of 0.5-2.2 ml/kg in 2 studies, and a fixed dose of 25 ml in a 3rd.

Because only a few pediatric studies have been published, a systematic evaluation of adverse events is difficult to perform. The risk of adverse events has been reported to be higher in adults than in children. Most studies of the risk of iohexol are associated with its use in radiologic or angiographic procedures in adults, where the usual dose is approximately 2 ml/kg body weight. A study of contrast nephropathy in azotemic diabetic adults being evaluated for coronary artery disease (Manske et al, Am J Med (1990); 89: 615-620) utilizing a mean dose of 31 ml of radio contrast (iohexol or iopamidol) in 59 patients with severe renal impairment (mean creatinine clearance 14+/-5 ml/min) showed that the risk of acute contrast nephropathy (defined as serum creatinine measured 48 hours after angiography greater than 25% above baseline) was associated with the dose of radiocontrast. In those subjects receiving < 20 ml of radiocontrast, 20% of subjects had a significant increase in creatinine (>25% above baseline) but none developed acute renal failure or required dialysis. This high risk group of adult patients received a much higher dose of iohexol than we propose, and had worse renal function than our cohort, as well as the multiple complications of diabetes and heart disease.

Additionally, we report below specific information from the package insert for iohexol from GE Healthcare describes side effects of the drug used in doses used for radiographic procedures in pediatrics. These doses range from1ml/kg OMNIPAQUE 300, to 5.0 ml/kg up to a total maximum volume of 250 ml OMNIPAQUE 300 or 6.0 ml/kg up to a total volume of 291 ml of OMNIPAQUE 300. The dosage recommended for use in children for contrast enhanced computed tomographic head imaging is 1.0 ml/kg to 2.0 ml/kg to a maximum dose of 28 g I with OMNIPAQUE 240 or 35 g I with OMNIPAQUE 300. At these doses **which are up to 50 times higher than the dose of 5 ml which we propose to use in the CKiD GFR study**, adverse events in 391 pediatric patients in controlled clinical trials of iohexol as a radiocontrast agent were generally less frequent than with adults. Reported adverse events included cardiovascular system events; including ventricular tachycardia(0.5%), 2:1 heart block (0.5%), hypertension (0.3%), and anemia (0.3%); nervous system events: pain (0.8%), fever (0.5%), taste abnormality(0.5%), and convulsions (0.3%). Respiratory system events include congestion (0.3%) and apnea (0.3%). GI system events include nausea (1%), hypoglycemia (0.3%), and vomiting (2%).

Finally, we can report on our use of the iohexol GFR through November 2013. We routinely monitor vital signs before and ten minutes after the 2 minute iohexol infusion. Our investigators had performed 2355 iohexol GFR studies by infusing 5 ml OMNIPAQUE 300 into subjects aged 1.5 to 19 years of age. There have been no serious adverse events to date. The attached slide shows that there were 20 adverse events (primarily changes in blood pressure or heart rate or a rash) that occurred in association with the iohexol infusion. In addition there were some complaints of nausea, numbness at the infusion site, and abdominal or back pain. Approximately half of the events were “probably” related to iohexol.

In light of this review, we feel that the risks associated with 5 ml of iohexol (Omnipaque300) are minimal.