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Evaluation of Tc-99m-DTPA for Renal Clearance Studies in the Pig

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Summary. Conventional creatinine clearance studies in the pig are complicated by difficulties with catheterisation, infection, accurate collection and active creatinine renal tubular reabsorption. We compared a single injection, ^{99m}Tc-DTPA elimination method with creatinine clearance. Nineteen pairs of GFR estimations were performed in 10 pigs: 7 in normal pigs and 12 following bile duct ligation and/or nephrectomy. Red cell and plasma protein binding of the isotope and its hepatobiliary excretion was assessed. Absolute and weight normalised endogenous creatinine clearances correlated significantly with ^{99m}Tc-DTPA elimination. ^{99m}Tc-DTPA red cell binding and hepatobiliary excretion were negligible. Thus, ^{99m}Tc-DTPA elimination is a valid indicator of changes in renal function in grouped porcine studies, particularly in the biliary obstruction model. However, isotope plasma protein binding was high in the 2 normal pigs assessed. Individual accuracy would be improved by routine protein binding correction, unless consistently low for a particular preparation.

Key words: Pig – Kidney function tests – Isotope – Clearance studies – Glomerular filtration rate

Introduction

The pig is used increasingly in biomedical research [6, 27] and particularly in surgical research. However, an ideal method for determining glomerular filtration rate (GFR) in this animal remains to be found.

The conventional endogenous creatinine clearance is limited by difficulties associated with urinary catheterisation, urinary collection [30] and introduction of sepsis. Also, creatinine clearance is at most an approximation, as the porcine renal tubule actively reabsorbs creatinine [17, 19, 26]. (Even so, endogenous creatinine clearance in the pig has been shown to correlate with the more accurate, but time-consuming inulin-clearance estimation [10].)

Thus, a "plasma-only" single injection isotope method for GFR estimation is attractive as it obviates the need for urinary catheter insertion. Also, direct quantitation of radioactive concentration is simpler than creatinine or inulin chemical assay. However, although ^{125}I-iodothalamate and ^{51}Cr-labelled ethylenediaminetetraacetate (EDTA) have acquired the status of secondary standards to inulin for GFR measurements in man [2, 15], they have disadvantages in experimental animals because of the long physical half life (60.0 and 27.7 days respectively). This leads to error when multiple estimations in a short period are performed, due to residual background activity. It also adds to handling safety problems.

^{99m}Tc-labelled diethylenetriaminepentaacetate (DTPA) has a much shorter half life (6 hours). It has been used to determine GFR in the pig [21], but still requires validation against more standard methods of GFR estimation and a number of sources of error require investigation.

This study was therefore performed to correlate plasma clearance of ^{99m}Tc-DTPA with endogenous creatinine clearance and also to examine red cell binding, plasma protein binding and hepatobiliary excretion of ^{99m}Tc-DTPA in the pig. The study was designed to encompass the range of GFR likely to be encountered in the normal animal and those in which renal function was compromised either by obstructive jaundice, nephrectomy or contralateral segmental renal artery ligation.

Materials and Methods

Eleven young female hybrid pigs (age 2 to 3 months) weighing 15 to 25 kg (median 21 kg) of Landrace and Large White stock were used. Approval by the Animal Ethics Review Subcommittee of the University of Cape Town was given for the study in accordance with the guidelines set down by the South African Medical Research Council. Nineteen paired clearance determinations were performed in 10 of the 11 pigs, measuring ^{99m}Tc-DTPA and creatinine clear-

Table 1. Surgical procedures performed in addition to arterial, venous and urinary catheterisation

Procedure	*n*	Days postoperatively of G.F.R. estimation
B.D.L. + H.S.V.	2	1, 1, 8, 8, 15, 15
B.D.L. + H.S.V. + nephrectomy	2	1, 5
Nephrectomy + segmental contralateral renal artery ligation	1	1, 4
Nephrectomy	1	7
B.D.L. + H.S.V. + biliary catheter	3	9

B.D.L. = bile duct ligation, H.S.V. = highly selective vagotomy

ance each time. In the remaining pig, only hepatobiliary isotope excretion studies were performed.

All pigs were anaesthetised with intravenous Pentothal induction, and maintained with a nitrous oxide, oxygen and halothane mixture given via a cuffed endotracheal tube using a Magill type circuit with I.P.P.R. Eight French calibre P.V.C. catheters were inserted in the internal jugular and external carotid vessels via a lateral cervical incision. Transurethral catheterisation was performed in 4 pigs or, because of technical difficulties, via suprapubic cystostomy (5 pigs). One pig, which also had a nephrectomy plus contralateral segmental renal artery ligation, had an 8 French ureteric catheter inserted to minimise the effect of bladder dead space on urinary volume estimation, a low urinary output being anticipated. This method of catheterisation was not used routinely however, because of an increased probability of ascending infection.

Additional surgical procedures were performed in 9 of the 11 pigs (see Table 1). In 4 this was at the time of urinary and vascular catheterisation, but in 5, a separate general anaesthetic was administered. The aim of these procedures was to produce a spectrum of partial renal impairment or to provide a route for bile collection. Aseptic techniques and a midline abdominal incision were used. In particular, the "biliary catheter" referred to in Table 1, was an 8 French latex rubber T-tube inserted into the common bile duct proximal to its point of ligation just above the duodenum. Highly selective vagotomy (HSV) was added following bile duct ligation, to prevent bleeding from gastric ulceration [28]. It was performed by ligating and dividing the vessels and nerves along the lesser curve of the stomach from the oesophagogastric junction to a point approximately 2 cm proximal to the pylorus.

Postoperatively the pigs were housed in individual cages and maintained on 100 mls/kg/day of intravenous Plasmalyte B[1], which was ceased when tolerating standard laboratory chow and water, provided ad lib. Patency of neck catheters was maintained by daily irrigation with heparinised saline.

The two methods of GFR estimation were performed concurrently in 7 catheterised, but otherwise normal, pigs and 12 times in 7 of the 9 pigs in which the operations shown in Table 1 were performed. All clearance measurements were carried out on unanaesthetised animals when they were in a stable state, at least 24 h postoperatively.

Method of Creatinine Clearance Estimation

Two 2h urine collections were performed with the bladder being washed with 30 ml saline at the start of each collection. Five ml of blood were taken for plasma creatinine determination at the beginning and end of each 2 h period. Creatinine was determined in urine and protein-free plasma filtrate by the Jaffe reaction using alkaline picrate. If the urine output was less than 20 ml per 2 h period, the set of results was excluded as being inaccurate. [The dead space in this bladder-catheter system is approximately 3 ml (as calculated in the sheep by Bishara and Bray [1]). This then would exceed 10% of the total volume and create a corresponding error in clearance estimation.]

Method for Tc-DTPA Clearance

Four mCi (148 MBq) of Byk-Mallinckrodt ^{99m}Tc-DTPA was injected into the jugular vein at time zero, which was during the period of creatinine clearance estimation. This Byk-Mallinckrodt preparation, as used by Robbins in the pig [21], is claimed generally to have > 95% of Tc99m bound to DTPA. It was injected within 1 h of preparation of the chelate.

Nine heparinised blood samples were taken from the carotid artery at 5, 10, 15, 20, 40, 60, 80, 100 and 120 min intervals post injection. One half millilitre aliquots of plasma were pipetted in duplicate and counted in a Nuclear Enterprices NE612 gamma counter for 5 min using a window specially adjusted for technetium-99m.

Plasma background samples were also counted together with duplicate 0.5 ml aliquots of a ^{99m}Tc-DTPA standard. The plasma disappearance curve was integrated from time zero to time infinity by computerised biexponential fit.

Determination of Red Cell Binding

Six times in 3 pigs, an additional 4 ml of heparinised whole blood was taken at 2 h post-injection for determination of red cell uptake of ^{99m}Tc-DTPA. Duplicate 0.5 ml aliquots of heparinised blood and plasma were pipetted into plastic counting tubes and counted for 5 min in the NE 1612 gamma counter. Percentage red cell binding was then calculated by the following formula:

$$\text{RCB} = \frac{b - [p(1 - \text{Hct})]}{b} \times 100\%$$

where RCB = red cell binding (%), b = blood radioactivity in counts per ml per second, p = plasma radioactivity in counts per ml per second, Hct = fractional microhaematocrit.

Determination of Plasma Protein Binding

Plasma protein binding was measured in two normal pigs at 1 h and 2 h after injection of 4 mCi (148 MBq) of ^{99m}Tc-DTPA into the jugular vein. Five ml heparinised blood samples were taken

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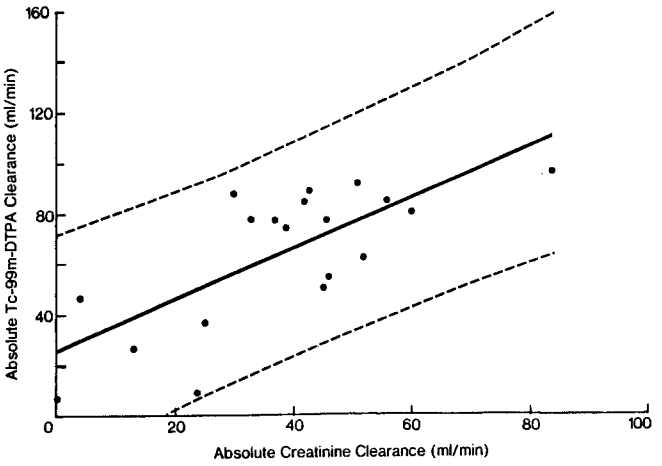

Fig. 1. Linear regression diagram correlating absolute Tc-99m-DTPA (Y) and creatinine (X) clearances. Nineteen paired estimations were obtained from 10 pigs. $Y = 25.21 + 1.02\,X$, $s = 19.44$, $r = 0.73$, $p < 0.001$. —— denotes regression line. – – – denote 95% confidence limits for an individual Y value at a given value of X

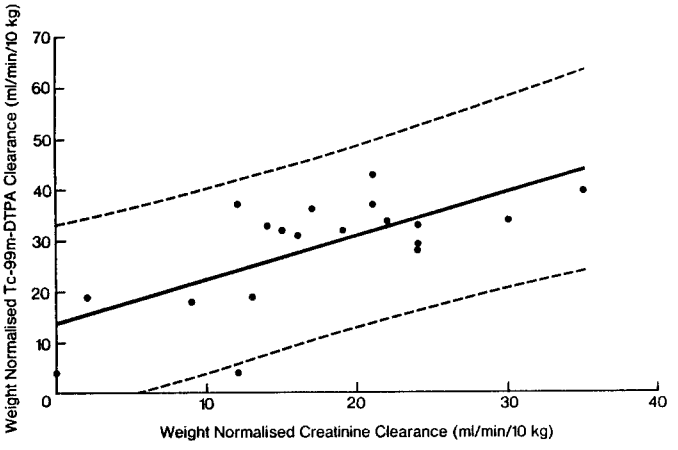

Fig. 2. Linear regression diagram correlating weight normalised Tc-^{99m}-DTPA (Y) and creatinine (X) clearances. Nineteen paired estimations were obtained from 10 pigs. $Y = 13.54 + 0.87\,X$, $s = 8.23$, $r = 0.68$, $p < 0.01$. —— denotes regression line. – – – denote 95% confidence limits for an individual Y value at a given value of X

at these times via a carotid line. The method used to measure protein binding was based on ultrafiltration and used an Amicon MPS-1 centrifugal micropartition system with Amicon YMT membrane filters, according to the manufacturers instructions. Centrifugation conditions for the ultrafiltration cells were 20 min at 1578 RCF. One tenth millilitre samples of plasma and plasma ultrafiltrate were pipetted into plastic tubes and counted for 10 min in the NE 1612 gamma counter. Results were corrected for the increased water content of the plasma ultrafiltrate relative to the original plasma [16] taking the average water plus crystalloid fractional content of pig plasma as 0.94 [15].

Determination of Biliary Excretion of Isotope

The amount of ^{99m}Tc-DTPA eliminated in bile during the first 2 h after injection was determined 6 times in 3 pigs. The total volume of bile collected was accurately measured and 0.5 ml duplicate aliquots of bile were pipetted into plastic tubes and counted for 5 min together with duplicate ^{99m}Tc-DTPA standards in the NE 1612 gamma counter. Hepatobiliary elimination of ^{99m}Tc-DTPA in 2 h was calculated as a percentage of the injected dose.

Statistical Analysis

The estimated correlation coefficient, and a 95% confidence interval for it, was calculated for both absolute and weight normalised ^{99m}Tc-DTPA and creatinine clearances. Linear regression of ^{99m}Tc-DTPA clearance on creatinine clearance was performed and the 95% confidence interval also given for an individual value of ^{99m}Tc-DTPA clearance at a given value of creatinine clearance [25]. Polynomial regressions up to order 3 were done. Calculations were performed using the Minitab[2] software package on a Prime mainframe computer. Data was expressed as the mean ± standard error of the mean, unless otherwise specified.

Results

Absolute ^{99m}Tc-DTPA vs Creatinine Clearances

The results from 19 tests on 10 pigs gave a sample correlation coefficient $r = 0.73$ with the 95% confidence interval for the population correlation coefficient being $0.42 < P < 0.89$. The linear regression analysis is depicted in Fig. 1. Polynomial regressions showed no significant improvement over linear regression. There may have been imprecision in the creatinine clearance determination as the duplicate values from the 2 x 2 h urine volume collections had a large spread.

Weight Normalised ^{99m}Tc-DTPA vs Creatinine Clearance

Similarly, the results gave a sample correlation coefficient of $r = 0.68$ with a 95% confidence interval for the population correlation coefficient being $0.33 < P < 0.87$. The linear regression analysis is depicted in Fig. 2. Similarly, polynomial regressions showed no improvement.

GFR in "Normal" Pigs

The mean value of the weight normalised ^{99m}Tc-DTPA clearance in the 7 normal pigs measured was 34.8 ± 1.9 ml/min/10 kg and the mean value of the weight normalised endogenous creatinine clearance in the same 7 pigs was 24.5 ± 2.4 ml/min/10 kg.

[2] Statistics Department, 215 Pond Laboratory, Pennsylvania State University, University Park, PA 16802, USA

Table 2. Reported GFR values in young large breed pigs

Group	Agent	GFR ± S.E.M. (ml/min/10 kg)	Breed	Age	Weight	No. of animals
Gyrd-Hansen (1968) [10]	Inulin	21 ± 0.5	Danish Landrace (Farm A)	3–8 months	28–123 kg	14
Gyrd-Hansen (1970) [11]	Inulin	30 ± 2.0	Danish Landrace (Farm B)	Not specified		5
Fahraeus et al. (1974) [6]	^{51}Cr-EDTA Inulin	38.2 ± 1.0 41.5 ± 1.0	Swedish Landrace, Swedish Yorkshire Race and crosses of above	10–14 weeks	16.5–28 kg	18 4
Friis (1979) [8]	Inulin	30 ± 2.0	Danish Landrace	8 weeks	15.3 ± 0.4 kg (Mean ± S.E.M.)	7
Mercer et al. (1979) [17]	^{125}I Sodium Iodothalamate	53.3 ± 1.2	"Cross Bred"	8–16 weeks	13–40 kg	46
Present Series	^{99m}Tc-DTPA	34.8 ± 1.9	Landrace and large white cross	2–3 months	15–25 kg	7

Red Cell Binding

The percentage red cell binding of ^{99m}Tc-DTPA at 2 h post-injection was measured 6 times in 3 pigs and included 2 measurements in 2 normal pigs. The values obtained for red cell binding ranged from 0% to 4.2% (median = 0%).

Plasma Protein Binding

Apparent binding of ^{99m}Tc-DTPA to plasma protein was found in the 2 normal pigs investigated. The percentages bound were 16.6 and 29.8 at 60 min and 24.3 and 30.7 at 120 min. The GFR, when corrected for protein binding in these normal pigs, was 41.4 and 47 ml/min/10 kg respectively.

Hepatobiliary Excretion of ^{99m}Tc-DTPA

This was very small in the first 2 h post-injection being less than 0.1% (range = 0 to 0.066%) of the injected dose in the 6 measurements performed in 3 pigs. In the two normal pigs investigated, the amount of ^{99m}Tc-DTPA cleared from the plasma in the same 2 h period was 81.9% and 81.3%.

Discussion

The relative figures given above for weight normalised ^{99m}Tc-DTPA and creatinine clearances in normal pigs; 34.8 and 24.5 ml/min/kg respectively; are consistent with the tubular reabsorption of creatinine in pigs [17, 19, 26] and the presence of non-creatinine chromogens in pig plasma.

The value of 34.8 ± 1.9 ml/min/10 kg for ^{99m}Tc-DTPA clearance obtained by us lies well within the 21–54 ml/min/10 kg range of GFR values reported by other investigators (Table 2). The inulin clearance values reported in the first study of Gyrd-Hansen [10] are at the lower limit of this range. However, the pigs used in this investigation were on average older than in the other studies summarised in the table and the mean GFR value may have been depressed by obesity in the larger and older animals. The value for ^{125}I sodium iodothalamate clearance of 53.3 ± 1.2 ml/min/10 kg reported by Mercer et al. [17] is appreciably higher than other reported values for GFR, but details of the breed and sex of the pigs investigated are not reported in this study and no comparison of iodothalamate clearance was made with any other GRF agent. The variability between the other studies may also be due to differences in age [8], breed or strain of pigs [11], or to experimental method. In our study, when correcting for protein binding, the values obtained in 2 pigs were similar to those obtained by Fahraeus et al. [6] using inulin in animals similar in size to ours.

The present study provides evidence that the ^{99m}Tc-DTPA clearance is a diagnostically useful measure of GFR in pigs when using grouped data. A good correlation between ^{99m}Tc-DTPA and endogenous creatinine clearance has been established within the range tested. Porcine red cell binding and hepatobiliary excretion of ^{99m}Tc-DTPA have been shown to be negligible. However, the wide 95% confidence interval for a value of ^{99m}Tc-DTPA clearance for any given value of creatinine clearance, questions the usefulness of our method when assessing individual variation in GFR. Correction of various potential sources of error may improve its usefulness.

Differences in correlation may be due to variability in both methods. Gyrd-Hansen [10] has shown variability to be greater with creatinine clearance than with the

inulin clearance, so reflecting possible fluctuations in creatinine reabsorption [19] and non-creatinine chromogens in pig plasma. Urinary volume estimations were also open to error, but these would affect inulin and creatinine clearance similarly. In the present series of normal pigs, the standard error in creatinine clearance estimation was slightly greater than for ^{99m}Tc-DTPA and the spread of the duplicate values from the 2 x 2 h urine volume collections was large. It has been shown elsewhere [30] that the main source of error in the measurement of renal clearances lies in the urine collection. It would, therefore, appear that ^{99m}Tc-DTPA elimination, which does not involve urine collection, is a more reproducible method, although this too has inbuilt sources of error. In man it has been shown [3] that ^{99m}Tc-DTPA clearance values vary slightly, depending on the commercial source of the agent, when compared with ^{51}Cr-EDTA clearance as reference method. In that comparative study only one preparation out of four yielded results identical to those obtained with ^{51}Cr-EDTA whereas the others underestimated GFR to a varying degree. Subsequently, the best of these ^{99m}Tc-DTPA preparations was shown [20] to give plasma clearance values which correlated well with the renal clearance of inulin, but overestimated GFR by 3.5 ml/min on average. In vivo plasma protein binding was assessed by Russell et al. [23], who investigated three commercial sources of ^{99m}Tc-DTPA in humans and demonstrated appreciable binding in two of these preparations.

The ^{99m}Tc-DTPA used in the present study showed appreciable binding to porcine plasma protein at one and two hours post-injection for the two normal pigs investigated. The measured binding (24.3% and 30.7% at 120 min post-injection) is in fact comparable in magnitude to that illustrated in humans by Russell et al. [23] in one of the preparations. However, there are several factors which may have contributed to the ultrafiltration method, which we used to measure protein binding, giving erroneously high results. Firstly, we performed centrifugation at 1 °C and not porcine body temperature. Hays and Green [12] showed that pertechnetate binding was sharply temperature dependent and increased in the cold. A similar phenomenon may occur with ^{99m}Tc-DTPA, or associated impurity, and pig plasma protein. Secondly, the "protein concentration effect" [9] due to continually rising protein concentration in the plasma compartment of the ultrafiltration cell may artificially enhance binding to a relatively small degree. The effect of the added heparin binding to ^{99m}Tc-DTPA is unknown, but assumed to be negligible.

It should be added that the ultrafiltration method, although agreeing with the gel filtration method [24] in assessing protein binding, unlike gel filtration, gives no information on the chemical identity of the bound technetium. The two usual impurities in ^{99m}Tc-DTPA are hydrolysed reduced technetium and pertechnetate [7]. Evidence exists suggesting that apparent ^{99m}Tc-DTPA binding measured may be due to one or both of these impurities which have become haemoconcentrated relative to ^{99m}Tc-DTPA at one and two hours post-injection. Hays and Green [12] showed that at 37 °C and pH 7.4, 65–80% of pertechnetate is normally bound to human serum proteins and Kempi and Persson [14] suggested that protein binding was correlated with the amount of "hydrolysed reduced" technetium found by gel filtration chromatography. Russell [23] reported that the ^{99m}Tc-DTPA preparation that gave minimal protein binding had lower levels of both impurities than the other two preparations assessed. Dayton et al. [4] showed that human pertechnetate clearance is on average only 13.5% of inulin clearance which suggests the concept of haemoconcentration of pertechnetate relative to ^{99m}Tc-DTPA. Specific organ uptake of pertechnetate by gastric mucosa, salivary glands and thyroid could counterbalance this effect to some extent.

Millar et al. [18] found that different batches of a technetium radiopharmaceutical kit from the one manufacturer (in this case Byk-Mallinckrodt as used by us) can have different stabilities. Under certain storage conditions of 3 h or longer, unacceptable levels of free pertechnetate of $> 5\%$ were obtained. The addition of the antioxidant para-aminobenzoate (as in Pentetate II[3]) may stabilise the ^{99m}Tc-DTPA complex by preventing reoxidation to pertechnetate. This reduces protein binding in vitro to $< 1\%$ [29] as well as reducing uptake of free pertechnetate by other organs, so eliminating these sources of error in measuring GFR.

Thus it is important that accurate and sensitive quality control either by thin-layer chromatography [7] or ion-exchange paper chromatography [24] should be carried out on the ^{99m}Tc-DTPA used in any future procine GFR determinations with close control of the time between kit preparation and analysis [13, 24]. The aim is a total impurity level $\leqslant 2\%$. The addition of a stabilizer should ensure that this level is maintained and that protein binding is minimal. Protein binding should be measured and corrected for initially with each new preparation until it can be shown to have consistently low protein binding. In comparative studies on the effect of surgical, radiotherapeutic or pharmacological intervention on porcine renal function, ^{99m}Tc-DTPA clearance, without protein binding correction, should still have value as an indicator of change in renal function. Such a development would parallel the increasing use of ^{99m}Tc-DTPA for investigating GFR alterations in man [5, 22].

Thus, the absence of significant hepato-biliary excretion, the range of renal function assessed and the avoidance of urinary catheterisation make ^{99m}Tc-DTPA clearance a potentially useful method in chronic porcine studies of renal function, especially in the presence of cholestasis.

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[3] Amersham International, Buckinghamshire, U.K.

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