Effects of Altered Physiologic States on Clearance and Biodistribution of Technetium-99m MAG_3, Iodine-131 OIH, and Iodine-125 Iothalamate

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Technetium-99m mercaptoacetyltriglycine ([^{99m}Tc]MAG_3) is a new renal radiopharmaceutical with biologic properties similar to iodine-131 orthoiodohippuric acid ([^{131}I]OIH). MAG_3 may be used as a replacement for [^{131}I]OIH and/or [^{99m}Tc]DTPA. For this reason, we compared the effects of several potential adverse clinical conditions on the clearance and biodistribution of MAG_3, OIH and a GFR marker. To simulate renal failure, five mice underwent bilateral renal pedical ligation. Twenty-four hours after surgery they were injected with MAG_3 and OIH and killed 2 hr postinjection. Compared to sham operated controls, liver activity for MAG_3 and OIH increased from 0.2% to 14.1% and 0.1% to 13.9%, respectively, while intestinal activity increased from 1.3% to 8.9% for MAG_3 and 0.2% to 7.7% for OIH. Constant infusion studies were performed in rats to evaluate the effects of increased plasma organic acid levels, mannitol diuresis, dehydration, and acid/base imbalance on the clearance of OIH, MAG_3, and [^{125}I]iothalamate. No differences were noted between the OIH and MAG_3 clearances following diuresis and dehydration and the differences involving acid/base imbalance were minimal. Dehydration depressed the clearance of [^{125}I]iothalamate more than that of OIH or MAG_3. Para-aminohippurate (PAH) infusion inhibited the clearance of MAG_3 more than OIH supporting proximal tubular transport for MAG_3; PAH had no effect on [^{125}I]iothalamate. In summary HPLC purified MAG_3 behaved similarly to OIH under adverse physiologic conditions and the data continue to support the use of MAG_3 as a potential clinical substitute for OIH.

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Technetium-99m mercaptoacetyltriglycine ([^{99m}Tc]MAG_3) is a new ^{99m}Tc renal radiopharmaceutical with biologic properties in animals similar to iodine-131 ortho-iodohippurate ([^{131}I]OIH) (*1,2*). MAG_3 purified by high performance liquid chromatography (HPLC) has also been shown to behave very similarly to OIH in normal volunteers and patients (*3–6*). A kit formulation has now been prepared and results in normal volunteers were similar to those obtained using the HPLC purified material (*7–8*). More extensive clinical trials with the kit formulation will soon be initiated and it is expected that this radiopharmaceutical will have widespread clinical use.

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A number of clinicians will probably use MAG_3 as a functional substitute for OIH, while others will undoubtedly use [^{99m}Tc]MAG_3 as a replacement for [^{99m}Tc]diethylenetriaminepentaacetic acid (DTPA) because of its more efficient extraction by the kidney and improved target to background ratios. In either case, it will be important to know the effects of commonly encountered clinical conditions on the biologic behavior of MAG_3 in comparison with standard agents. To address these questions, the biodistributions of OIH and MAG_3 were compared in a model of complete renal failure (renal pedical ligation). Studies were also conducted to determine the effects of elevated organic acid levels, acidosis, alkalosis, osmotic diuresis, and dehydration on the renal clearance, protein binding, and extraction efficiencies of MAG_3, OIH, and iodine-125 iothalamate.

MATERIALS AND METHODS

The synthesis and radiolabeling of the S-benzoate protected mercaptoacetyltriglycine is the subject of another report (*1*). Briefly, the ^{99m}Tc complex was formed by dissolving ~0.3 to 0.6 mg of the benzoate protected ligand in 100 μl of 1 N NaOH. Technetium-99m pertechnetate in generator saline (Mallinckrodt, St. Louis, MO or Cintichem, Tuxedo, NY) was added in volumes of ~1 ml. One milligram (100 μl of a 10 mg/ml solution) of freshly dissolved sodium dithionite (J. T. Baker Chemical Co., Phillipsburg, NJ) was added and the mixture was heated at 82°C for 5 min. Finally, the solution was neutralized by the addition of 1 ml of a 0.01*M* phosphate/1 % ethanol buffer at a pH of 7.0. Prior to use, the MAG_3 complex was purified by high performance liquid chromatography (HPLC) utilizing a 0.01*M* phosphate/4% ethanol pH 7.0 mobile phase on a 5-micron 4.6 mm × 250 mm C-18 ODS reverse phase column at a 1 ml/min flow rate. The retention volume for the MAG_3 complex was ~5 min.

Iodine-131 OIH was obtained commercially; the percent radiochemical purity in the preparations ranged from 96.5% to 98.5%. Iodine-125 iothalamate is cleared by glomerular filtration similar to [^{99m}Tc]DTPA (*9*) and was used as a glomerular filtration marker in these studies. Iothalamate labeled with ^{125}I by the method of Kato et al. (*10*) contained <1% free iodine.

ANIMAL STUDIES

Mouse Biodistribution Studies

A control and an experimental group of five female mice each were utilized in the biodistribution studies. All of the mice were anesthetized intraperitoneally with pentobarbital 0.65 mg/10 g body weight. In the experimental group of animals, two flank incisions were made on either side of the vertebral column and the renal pedicles were ligated 24 hr prior to the biodistribution study while the control group underwent a sham operation. Both groups of animals were allowed food and water ad lib and allowed to recover for 24 hr before a single intravenous tail vein injection containing 1 μCi of MAG_3 and 0.3 μCi of OIH in 0.1 ml was given. After injection the animals were placed in metabolic cages for urine collection and killed at 120 min postinjection. Selected organs, blood, and urine were counted in a dual channel well counter with corrections made for ^{131}I scatter into the ^{99m}Tc channel.

Rat Constant Infusion Clearance Studies

General animal preparation. Male rats weighing between 250 and 350 g were utilized for all constant infusion clearance studies; there were six animals in each experimental group. The animals were anesthetized with ketamine HCl (100 mg/kg IP) and placed on a heated surgical table. Following a tracheostomy, the left jugular vein was cannulated with two pieces of PE-50 tubing (one for infusion of the radiopharmaceuticals and one to infuse normal saline to maintain hydration). The right carotid artery was cannulated for blood sampling; the right jugular vein was cannulated with PE-50 tubing for the infusion of agents used to induce physiologic changes, and the bladder was catheterized utilizing heat flared PE-50 tubing. The core temperature of each animal was continually monitored throughout the study using a rectal temperature probe (VWR Digital Thermometer 500, San Francisco, CA).

The radiopharmaceutical agents ([^{99m}Tc]MAG_3, 10 μCi/ml; [^{131}I]OIH, 2 μCi/ml; and [^{125}I]iothalamate, 2 μCi/ml) were infused at a flow rate of 1.2 ml/hr for 45–60 min through the left jugular vein. A 5- to 10-min urine sample was collected for all clearance value determinations and the blood sample was drawn at the midpoint of the urine collection period. The urine for each clearance period was collected under water saturated oil. The blood samples (0.2 to 0.3 ml) were centrifuged for 10 min at 2,000 *G* and a plasma sample was obtained. Plasma clearance was determined utilizing the equation: CL = UV/P where CL is the plasma clearance in ml/min, U is the urine radioactivity concentration, V is the urine volume excreted per minute and P is the plasma radioactivity concentration. A 3-ml arterial blood sample was obtained for plasma protein binding determinations at the end of the last clearance period. The blood was centrifuged and 1 ml of plasma was placed into a micropartition membrane system (Centrifree Micropartition System, Amicon Corporation, Danvers MA) and centrifuged at 1,600 *G* for 10 min (*11*).

The samples were initially counted in a dual channel well counter (Beckman Gamma 5500, Fullerton, CA) for ^{99m}Tc and ^{131}I with corrections made for ^{131}I scatter into the ^{99m}Tc channel. The ^{99m}Tc was then allowed to decay to background and the samples were recounted for ^{125}I and ^{131}I with scatter corrections made for ^{131}I into the ^{125}I channel. Statistics were performed using the paired t-test or the t-test for independent samples.

Extraction efficiency. The animals were prepared as described above, however, the right jugular vein was not cannulated. After three successive 10-min clearance periods, a left renal venous blood sample was obtained followed by the 3-ml carotid arterial sample. Both blood samples were centrifuged to obtain a plasma sample. The extraction efficiency (EE) was calculated by measuring the difference between the arterial and venous blood sample: EE = (arterial concentration − venous concentration)/arterial concentration.

Mannitol diuresis. The animals were prepared as described in the general animal preparation section. After the control clearance was obtained, 250 mg of mannitol in 1 ml were injected intravenously through the right jugular vein. This injection was followed immediately by a mannitol infusion 75 mg/ml, at a rate of 2.6 ml/hr. The mannitol infusion was continued for 30 min followed by three experimental (diuresis) urine collection periods of 5 min each. Normal saline was co-infused through the left jugular vein to keep the animals hydrated during the study.

Dehydration. The rats were dehydrated for 24 hr prior to the study by withholding fluids although they were allowed food ad lib. The animals were surgically prepared as previously described except that the right jugular vein was not cannulated. The radiopharmaceutical agents were infused for a 60-min period at a flow rate of 1.2 ml/hr. Three 10-min urine collection periods were then obtained.

Acute acid imbalance. The animals were surgically prepared as previously described. At the end of the control clearance periods a freshly prepared 0.9*M* ammonium chloride solution was infused through the right jugular vein at a rate of 1.8 ml/hr for 45 min prior to the three 10-min urine collection periods. A 0.4-ml carotid blood sample was obtained during the midpoint of the control and the experimental clearance periods and a 0.1-ml sample of whole blood was immediately assayed for pH and pCO_2 using a blood gas analyzer (Radi-

TABLE 1
Biodistribution (% Dose/Organ) of [^{99m}Tc]MAG_3 and [^{131}I]OIH 2 hr Postinjection in Mice with Renal Pedicle Ligation*

Control Group*	Blood	Liver	Kidney	Stomach	Intestines	Urine
OIH	0.11 ± 0.02	0.12 ± 0.02	0.09 ± 0.13	0.60 ± 0.20	0.19 ± 0.01	91.24 ± 3.77
MAG_3	0.01 ± 0.01	0.16 ± 0.06	0.09 ± 0.13	0.03 ± 0.01	1.31 ± 0.35	91.47 ± 3.53
Experimental group*	**Blood**	**Liver**	**Kidney**	**Stomach**	**Intestines**	**Urine**
OIH	17.85 ± 1.02	13.87 ± 2.81	1.40 ± 0.13	1.60 ± 0.34	7.70 ± 0.84	0.13 ± 0.03
MAG_3	19.41 ± 1.94	14.06 ± 2.10	1.68 ± 0.19	0.98 ± 0.22	8.93 ± 2.90	0.18 ± 0.04

* Five mice per group; mean ± s.d.

ometer America BMS-3 Mk-2, Copenhagen, Denmark); urine pH was measured at the end of the study using a standard pH meter (Fisher Scientific, Springfield, NJ). The plasma bicarbonate levels were calculated based on the blood pH and pCO_2 levels.

Acute base imbalance. The animals were surgically prepared as described. At the end of the control measurements a freshly prepared 0.9*M* sodium bicarbonate solution was infused through the right jugular vein at a rate of 6 ml/hr for 40 min prior to obtaining the three 10-min experimental collection periods. As described under the acid imbalance study, a 0.4-ml arterial blood sample was obtained at the midpoint of each clearance period and a 0.1-ml sample was immediately assayed for pH and pCO_2 levels. Urinary pH was also measured at the end of the study.

Para-aminohippuric acid competitive inhibition. The animals were surgically prepared as described above. After two control clearance periods were obtained, PAH was infused through the right jugular vein at a rate of 50 mg/kg/hr for 30 min. Two 10-min clearances were obtained and the dose of para-aminohippuric acid (PAH) was then increased to 500 mg/kg/hr for 30 min again followed by two clearance periods. Stock solutions of 10 and 100 mg/ml of PAH were utilized for the two dose levels allowing PAH infusion rates between 1.25 and 1.75 ml/hr.

RESULTS

Mouse Biodistribution Studies

There is no difference in the ^{99m}Tc and ^{131}I blood liver, kidney, or intestinal activity following renal pedicle ligation (Table 1). The minimal renal and urine activity are probably secondary to capsular blood flow. Slightly more ^{131}I activity is present in the stomach compared with ^{99m}Tc but this finding was almost certainly a result of free ^{131}I in the [^{131}I]OIH preparation.

Plasma Clearance, Extraction Efficiency, and Protein Binding

The plasma clearance of OIH was slightly greater than that of MAG_3, 2.84 ml/min/100 g versus 2.62 ml/min/100 g, $p \leq 0.05$ (Table 2). Both agents were cleared significantly faster than the GFR marker, [^{125}I]iothalamate ($p < 0.01$). Protein binding for MAG_3 was greater than for the other two agents, but in spite of this finding the extraction efficiency of MAG_3 was still greater than that of OIH and [^{125}I]iothalamate ($p \leq 0.05$).

Mannitol Diuresis

There was no change in plasma clearance following mannitol diuresis (Table 3). Urine volume increased from 0.12 ± 0.03 ml/min to 0.57 ± 0.09 ml/min following diuresis. Plasma protein binding decreased by 68% for OIH, 49% for MAG_3, and 84% for iothalamate compared to the control group (Table 2). Because of the blood volume required, plasma protein binding was not measured in these animals following the control clearance periods and prior to mannitol diuresis.

Dehydration

Twenty-four hours of water deprivation resulted in a substantial fall in plasma clearances for all three agents compared to control values $P \leq 0.01$ (Table 4). Urine volume in the dehydrated rats was 0.006 ± 0.002 ml/min compared to 0.12 ± 0.03 ml/min in controls. Protein binding for OIH and iothalamate was decreased by 45–60% compared to control values but was essentially unchanged for MAG_3.

TABLE 2
Plasma Clearance (ml/min/100 g), Protein Binding, and Extraction Efficiency of [^{131}I] OIH, [^{99m}Tc] MAG_3, and [^{125}I]Iothalamate*

	[^{131}I]OIH	[^{99m}Tc]MAG_3	[^{125}I]Iothalamate
Plasma clearance	2.84 ± 0.46	2.62 ± 0.46	1.14 ± 0.23
% Protein binding	41% ± 6%	78% ± 4%	13% ± 6%
Extraction efficiency	74% ± 6%	82% ± 6%	31% ± 5%

* Six rats; mean ± s.d.

TABLE 3
Plasma Clearance (ml/min/100 g) and Protein Binding of [^{99m}Tc]MAG_3, [^{131}I]OIH, and [^{125}I]Iothalamate Following Mannitol Diuresis*

	[^{131}I]OIH	[^{99m}Tc]MAG_3	[^{125}I]Iothalamate
Control clearance	2.96 ± 0.27	2.65 ± 0.98	0.98 ± 0.07
Mannitol clearance	2.96 ± 0.35	2.65 ± 0.37	0.97 ± 0.13
Protein binding	24% ± 10%	42% ± 19%	5% ± 3%

*Six rats; mean ± s.d.

Acute Acid Imbalance

Following ammonium chloride infusion, there was a significant drop in the urine pH, blood pH, and bicarbonate concentration ($p \leq 0.01$; table 5). Compared to control values, OIH clearance decreased by 18%, MAG_3 by 27%, and iothalamate clearance by 30% ($p \leq 0.05$; Table 5). Compared to previous controls, OIH protein binding decreased by 27%, MAG_3 by 19%, and iothalamate by 31%, $p \leq 0.05$ (Table 2).

Acute Base Imbalance

Following sodium bicarbonate infusion, there was a significant rise in urine pH, blood pH, and bicarbonate concentration ($p \leq 0.01$; Table 6). There was no change in OIH clearance and a minimal reduction (8%) in MAG_3 clearance although the difference was not significant: iothalamate clearance decreased by 16% ($p \leq 0.05$). In all cases, protein binding decreased from 17–38% compared with controls.

PAH Inhibition

PAH infusion of 50 mg/kg/hr produced 11–16% decrease in the clearance of OIH and MAG_3 but did not significantly affect the iothalamate clearance ($p \leq 0.05$; Table 7). In contrast, infusion of 500 mg/kg/hr reduced the MAG_3 clearance by ~63% while it reduced OIH clearance by only 23% ($p \leq 0.01$); there was still no significant change in iothalamate clearance. In all cases, plasma protein binding was reduced ~50% (Table 8).

DISCUSSION

Compounds cleared by the kidneys by different mechanisms do not measure the same functional parameter and may be affected differently in different disease states (*12–14*). We previously showed that acute obstruction depresses iothalamate clearance much more than OIH clearance (*12*). Lee and Blaufox have reported that the renal clearance of [^{99m}Tc]DTPA is unaffected by probenecid and PAH but the renal accumulation of [^{99m}Tc]glucoheptonate is significantly reduced (*13*). In contrast, PAH and probenecid had no effect on the renal accumulation of [^{99m}Tc]dimercaptosuccinic acid (DMSA) but urine acidification decreased the renal uptake of DMSA by 50% and doubled the hepatic activity (*13,14*). These studies suggest that a changing biochemical or physiological status resulting in decreased kidney uptake, increased background activity, or a changing kidney to liver or background ratio could impair the clinician's ability to interpret sequential studies in a patient with underlying renal disease. The problems could theoretically be accentuated in patients with asymmetric renal disease.

Since MAG_3 will probably be widely used clinically, its clearance was compared to simultaneously administered OIH and [^{125}I]iothalamate under several altered physiologic conditions: renal pedical ligation, dehydration, diuresis, and acid/base imbalance. There was no significant difference in the clearance rates for MAG_3 and OIH under conditions of diuresis or a sodium bicarbonate loading. In the dehydrated animals, the clearances of both agents were decreased ~30% compared with controls, probably secondary to a decrease in renal blood flow and possibly an increase in intravascular osmotic pressure. Acidosis also significantly decreased the clearance of OIH, MAG_3, and iothalamate compared to control values. The decreased clearance associated with dehydration and acidosis would certainly lead to increased background activity and a decreased kidney/background ratio. In the clinical situation, severe acidosis or dehydration may well decrease the clearance of commonly used radiopharmaceuticals as well as decrease the 1–2 or 1–3 min kidney to background ratio. These effects need to be kept in mind in interpreting sequential renal studies.

Both probenecid (*1*) and PAH were found to block the renal clearance of MAG_3. Since these agents act on the enzyme systems of the proximal tubule, MAG_3 is probably transported to the tubular lumen by way of the proximal tubular cells (*15,16*). PAH and probenecid also blocked the clearance of OIH, although the effects were not as great.

TABLE 4
Plasma Clearance (ml/min/100 g) and Protein Binding Following 24 hr of Water Deprivation*

	[^{131}I]OIH	[^{99m}Tc]MAG_3	[^{125}I]Iothalamate
Plasma clearance	1.90 ± 0.26	1.79 ± 0.30	0.60 ± 0.14
Protein binding	41 ± 3%	83 ± 2%	12 ± 4%

*Six rats; mean ± s.d.; refer to Table 2 for control values.

TABLE 5
Plasma Clearance (ml/min/100 g) and Protein Binding of [^{99m}Tc]MAG_3, [^{131}I]OIH, and [^{125}I]Iothalamate Following Ammonium Chloride Infusion*

	[^{131}I]OIH	[^{99m}Tc]MAG_3	[^{125}I]Iothalamate
Control clearance	2.90 ± 0.31	2.71 ± 0.35	1.06 ± 0.08
Experimental clearance	2.43 ± 0.42	1.98 ± 0.28	0.74 ± 0.07
Protein binding	30 ± 7%	63 ± 11%	9 ± 3%
	Urine pH	Blood pH	HCO_3 (mEq/l)
Control	6.8 ± 0.2	7.38 ± 0.02	19.85 ± 2.13
Experimental	5.4 ± 0.3	7.19 ± 0.03	9.85 ± 1.54

*Six rats; mean ± s.d.

The fact that tubular blockage (increased organic acid concentration) had a greater effect on MAG_3 than OIH raised the possibility that MAG_3 may not be cleared as rapidly as OIH in patients with impaired renal function. Furthermore MAG_3 is structurally similar to DADS, a previously studied [^{99m}Tc]N_2S_2 renal agent with substantial hepatobiliary excretion in patients with renal failure (*17*). To evaluate this possibility, we compared the biodistribution and hepatobiliary elimination of MAG_3 and OIH in mice with renal pedicle ligation and found no significant differences in gut activity (Table 1). Similarly, preliminary results in patients with impaired renal function using HPLC purified MAG_3 have not demonstrated disproportionate hepatobiliary excretion (*4,5*).

In contrast to the previously reported clearance values in rats (*1*), the plasma clearance of MAG_3 was slightly, but significantly, less than OIH ($p \leq 0.05$). However, the clearance values reported in this paper were almost identical to those reported by the Müller-Suurs; 2.76 ml/min/100 g for OIH versus 2.53 ml/min/100 g for HPLC-purified MAG_3 (*18*). In the initial study (*1*), a weighed sample of whole blood was counted in a well counter with all of the ^{131}I and ^{99m}Tc activity assumed to be in the plasma, and the hematocrit was used to determine the plasma mass in the sample (*1*). This technique did not adequately account for OIH uptake into the red cells (*19*) and underestimated the OIH plasma clearance. In the current study, we separated the plasma from the red cells and counted the plasma directly. While plasma clearances provide a better physiologic comparison between the two agents, whole blood clearances may be more relevant from a clinical point of view since it is the whole blood clearance not the plasma clearance that determines how rapidly a radioactive tracer is cleared from the body.

Our extraction efficiency values—74% for OIH versus 82% for MAG_3—were not corrected for leakage of OIH or MAG_3 out of the red blood cells. These results differed slightly from the uncorrected extraction efficiency of 85% for OIH and 74% for HPLC-purified [^{99m}Tc]MAG_3 reported by the Müller-Suurs (*18*). The Müller-Suurs also reported that ~31% of the whole blood OIH activity in rats is associated with the red blood cells versus 11% for MAG_3. When they corrected for leakage from the rat red blood cells in the venous sample, the OIH extraction efficiency was estimated to be 99% versus 80% for MAG_3 (*17*). Further studies will be needed to clarify these differences.

Protein binding for all three agents was significantly reduced in all rat studies with the exception of dehydration. PAH infusion (500 mg) and mannitol produced a 50% reduction in protein binding for OIH and MAG_3 whereas acidosis and alkalosis produced a 25% reduction. There was a suggestion that this pattern held for [^{125}I] iothalamate but the differences between PAH,

TABLE 6
Plasma Clearance (ml/min/100 g) and Protein Binding of [^{99m}Tc]MAG/3, [^{131}I]OIH, and [^{125}I]Iothalamate Following Sodium Bicarbonate Infusion*

	[^{131}I]OIH	[^{99m}Tc]MAG_3	[^{125}I]Iothalamate
Control clearance	3.25 ± 0.55	2.85 ± 0.30	1.28 ± 0.10
Experimental clearance	3.22 ± 0.45	2.62 ± 0.37	1.07 ± 0.13
Protein binding	30% ± 3%	65% ± 5%	8% ± 4%
	Urine pH	Blood pH	HCO_3^- (mEq/l)
Control	6.6 ± 0.3	7.44 ± 0.03	19.50 ± 1.97
Experimental	9.1 ± 0.8	7.74 ± 0.05	46.88 ± 2.07

*Six rats; mean ± s.d.

TABLE 7
Effect of PAH Infusion of the Plasma Clearance and Protein Binding of [^{99m}Tc]MAG_3, [^{131}I]OIH, and [^{125}I]Iothalamate

	[^{131}I]OIH	[^{99m}Tc]MAG_3	[^{125}I]Iothalamate
Control	3.36 ± 0.48	3.04 ± 0.33	1.09 ± 0.11
50 mg/kg/hr of PAH	2.99 ± 0.43	2.55 ± 0.23	1.03 ± 0.07
% of Control	88% ± 8%	84% ± 7%	95% ± 11%
500 mg/kg/hr of PAH	2.58 ± 0.47	1.14 ± 0.14	1.02 ± 0.13
% of Control	79% ± 9%	38% ± 4%	95% ± 11%
Protein binding	20% ± 7%	44 ± 13%	7% ± 4%

mannitol, and acid and base imbalance were not significant. For comparison, Lee and Blaufox reported that dehydration, mannitol, probenecid, urine acidification, and PAH all reduced the protein binding of glucoheptonate from ~47% to 34%; in their study protein binding was unaffected by urine alkalinzation (*13*). Regardless of the degree of protein binding, it does not appear to affect the tubular extraction of [^{99m}Tc]MAG_3.

In summary, MAG_3 behaves very similarly to OIH under a variety of altered physiologic and biochemical conditions. These data continue to support the potential utility of MAG_3 as a clinical substitute for OIH. While preliminary results in animals and human subjects suggest that the plasma clearance of MAG_3 is less than that of OIH, the rate of renal uptake and urinary excretion of the two agents is almost identical because of the smaller volume of distribution (higher plasma concentration) of MAG_3 and the fact, that unlike OIH, very little MAG_3 enters the red blood cell (*1–8,17*). The percent uptake of MAG_3 and OIH in the kidney between 1–2 or 1–3 min postinjection appears to be almost identical (*3,4,7*) and it is interesting to note that techniques which measure clearance indirectly based on the percent injected dose in the kidney at 1–2 or 1–3 min postinjection will obtain almost identical valves for MAG_3 and OIH; different nomograms for MAG_3 and OIH could be used to convert similar uptakes into different clearances. Finally, even though the clearance of MAG_3 is less than OIH, there may be a relatively constant relationship between the two clearances and the clinical value of the two measurements may be equivalent. These issues will need to be addressed in future studies.

TABLE 8
Effect of Physiologic Alterations on the Percent Protein Binding

	[^{131}I]OIH	[^{99m}Tc]MAG_3	[^{125}I]Iothalamate
Control	41 ± 6	78 ± 4	13 ± 6
500 mg PAH	20 ± 7	44 ± 13	7 ± 4
Mannitol	24 ± 10	42 ± 19	5 ± 3
Dehydration	41 ± 3	83 ± 2	12 ± 4
Ammonium chloride	30 ± 7	63 ± 11	9 ± 3
Sodium bicarbonate	30 ± 3	65 ± 5	8 ± 4

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