CUSTODIOL®

Bretschneider HTK Solution
For Kidney, Liver, Pancreas and Heart Preservation

P08-0735

Description

Composition

1.000 ml CUSTODIOL® contain:

0.8766	g	Sodium chloride	=	15.0	mmol/l
0.6710	g	Potassium chloride	=	9.0	mmol/l
0.1842	g	Potassium hydrogen 2-ketoglutarate	=	1.0	mmol/l
0.8132	g	Magnesium chloride · 6 H_2O	=	4.0	mmol/l
3.7733	g	Histidine · HCl · H_2O	=	18.0	mmol/l
27.9289	g	Histidine	=	180.0	mmol/l
0.4085	g	Tryptophan	=	2.0	mmol/l
5.4651	g	Mannitol	=	30.0	mmol/l
0.0022	g	Calcium chloride · 2 H_2O	=	0.015	mmol/l

in sterile Water for injection
Anion: Cl^- 50 mval

Physical Properties

pH 7.02 - 7.20 at 25ºC (77° F) [pH 7.4 - 7.45 at 4ºC (39.2° F)]
Osmolality: 290 mosmol/kg

Caution: Federal law restricts sale of this device to or on the order of a physician or licensed practitioner.

Indications for Use

CUSTODIOL® HTK solution is indicated for perfusion and flushing of donor kidneys, liver, pancreas and heart prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation to the patient. CUSTODIOL® HTK solution is not indicated for continuous machine perfusion of donor organs.

essential pharmaceuticals, LLC

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Warnings and Precautions

Warning: Perfusion of the kidney, liver, pancreas and/or heart should be carried out with a maximum hydrostatic pressure of 120 mmHg.

Warning: CUSTODIOL® is not indicated for intravenous or intraarterial administration. It is indicated only for selective perfusion of the kidney, liver, pancreas and heart and for cooling of the surface areas, i.e., for the preservation of the donor organ during the transport from donor to recipient. CUSTODIOL® may not be used for systemic infusion.

Warning: CUSTODIOL® is not indicated for continuous perfusion.

Warning: Keep out of reach of children.

Caution: The product must be used before the expiration date stated on the package.

Caution: The product must be stored according to the recommendations prior to use.

Adverse Events

No side effects have been encountered that could be attributed to this product.

Intended User

CUSTODIOL® must be used in medical facilities by trained and skilled medical personnel only.

Indication of the target population

CUSTODIOL® HTK Solution is indicated for perfusion and flushing of donor kidneys, liver, pancreas and heart prior to removal from the donor or immediately after removal from the donor. CUSTODIOL® HTK Solution is not indicated for continuous machine perfusion of donor organs.

The safety and efficacy of CUSTODIOL® HTK Solution as an organ preservation solution has not been clinically demonstrated in extended criteria donors (ECD), donation after cardiac arrest (DCD) or other marginal donor populations.

Interactions with other Medical Products

Interactions with such therapeutic agents as glycosides, diuretics, nitrates, antihypertensives, beta blockers and calcium antagonists, which are used perioperatively, have not been reported.

Overdoses (Symptoms, Countermeasures)

In the case of entry of the HTK solution into the general circulation, the resultant change in the concentration of sodium and calcium are very slight. After checking sodium and calcium levels in the extracorporeal circulation both of these electrolytes should be replaced if necessary.

Instructions for Use (Recommendations)

Required Equipment:

Perfusion apparatus with a Y-piece for bottle or bags
Perfusion cannula tube 2.5 to 3 mm
Tube clamp
Perfusion stand with a height setting of up to 200 cm with tape measure.
Cooling Equipment (5 to 8°C) for use in cardiac surgery
Perfusion tube with an internal diameter of 6 mm
Transport Container with sterile pouch for transport of the cooled organ from donor to recipient.

Filtration of CUSTODIOL® is not necessary or recommended.

Tolerance of Ischemia by the Kidney

The kidney may be stored with ice cold CUSTODIOL® solution at about 2 to 4°C with a period of (cold) ischemia of up to 48 hours. Warm ischemia time, that is to say the average time period required for the completion of anastomosis of the vessels, is usually 30 minutes.Taking this time as a basis, the organ recovers completely with optimal immediate function within 24 hours.

Tolerance of Ischemia by the Liver

The liver may be stored with ice cold CUSTODIOL® solution at about 2 to 4°C with a period of (cold) ischemia of up to 15 hours. Warm ischemia time, that is to say the average time period required for the completion of anastomosis of the vessels, is usually 30 minutes. Taking this time as a basis, the organ recovers completely with optimal immediate function within 24 hours.

Tolerance of Ischemia by the Pancreas

The pancreas may be stored with ice cold CUSTODIOL® solution at about 2 to 4°C with a period of (cold) ischemia of up to 15 hours. Warm ischemia time, that is to say the average time period required for the completion of anastomosis of the vessels, is usually 30 minutes.

Tolerance of Ischemia by the Heart

The heart may be stored with ice cold CUSTODIOL® solution at about 2 to 4°C with a period of (cold) ischemia of up to 4 hours. Warm ischemia time, that is to say the average time period required for the completion of anastomosis of the vessels, is usually 30 minutes.

Introduction of Renal Perfusion

Following successful laparotomy, the kidney is prepared by ligature of the capsular vessels.The perfusion catheter for selective kidney perfusion is fixed in the renal artery using a tourniquet. Cold perfusion (2-4°C) is performed under hydrostatic pressure (maximum of 120 mmHg). Within the first minute of perfusion, the renal

vein is incised and clamped off adjacent to the vena cava. The escaping perfusate is removed from the abdominal cavity. After approximately 10 minutes of perfusion, the kidney is resected before transplantation.

Introduction of Hepatic Perfusion

The donor should be heparinised appropriately, and the aorta or the iliac bifurcation and the portal vein will be exposed. The perfusion tubing should be of the largest possible diameter and the cannulae should have an internal bore of at least 5 mm. Because of the low viscosity of the solution, perfusion is performed under hydrostatic pressure only (maximum of 120 mmHg). Perfusion of the portal vein can be performed by cannulating the superior or inferior mesenteric vein and advancing the catheter up to the origin of the portal vein. After performing cannulation, clamping off the aorta and opening the vena cava, bubble-free perfusion is begun via both lines simultaneously. As a general rule, 8-12 liters of HTK at 2-4°C should be perfused (about 300 ml per kg of body weight) and this will require about 10 minutes.

Should the center decide to use the so-called aorto-single flush technique, the total amount of the preservation solution needed is perfused only via the aortal line. Once again, a pressurized infusion is not necessary or recommended. A Y-perfusion system is recommended in addition to perfusion tubing of the largest possible caliber and perfusion cannulae with an internal bore of at least Charrière 15 (5 mm). The time required for perfusion is extended by about 5 minutes.

At the implant site, the back-table preparation includes the reperfusion of approximately 500 ml cold HTK solution. The perfusion is stopped when the anastomoses of the inferior vena cava are completed at the end of the second warm ischemia time. It is permissible, in view of the flow properties and low potassium concentration of the HTK solution, to perform flushing of the organ or testing for leaks in the anastomoses with HTK solution itself, if necessary. Alternatively, any standard flushing solution may be used. Simultaneous reperfusion via the artery and the portal vein are preferable, though primary reperfusion through the portal vein alone is acceptable.

Introduction of Pancreatic Perfusion

There are two important considerations for perfusion of the pancreas. First, the pancreas is a low-flow organ and can be damaged by hyperperfusion. Secondly, even the gentlest manipulations can cause edema. Failing to allow for these factors can produce not only impairment of endocrine function, but perhaps more seriously, can cause damage to exocrine function and result in reperfusion pancreatitis.

When removing the pancreas, the surgeon must first of all assure adequate arterial perfusion via the celiac trunk, the splenic artery and the pancreaticodorsal artery (if present), together with the superior mesenteric and gastroduodenal arteries. Secondly, venous drainage must be safeguarded either by opening the portal vein, the inferior mesenteric vein, or the splenic vein at the hilum of the spleen, or by the physiological outflow into the portal vein drainage area. In practice, it is considered advisable, after appropriate dissection and exposure of the abdominal aorta, the vena cava, and the aorta above the celiac trunk, to divide the inferior mesenteric artery between ligatures, to clamp off the aorta below the diaphragm and then to run a total of 10 liters HTK into the distal part of the aorta, so as to perfuse the liver, pancreas, and the kidneys. The solution is perfused under gravity with the fluid level 1.5 meters above the heart. At this stage the mesenteric root should not be divided distal to a TA stapler suture, so that by perfusing the small intestine, the liver can be perfused via the portal vein. This will not only accelerate liver cooling, but will also provide a safeguard against overperfusion of the pancreas. After dividing the mesenteric root, the surgeon can then sever the mesocolon and the splenocelic ligament, separating the entire small and large intestine caudally. This will make surface cooling even more effective.

Introduction of Cardiac Perfusion

The inactivation of the heart renders it susceptible to overstretching. Decompression of the left ventricle must therefore be performed at the commencement of cardioplegia. For adult hearts the following recommendation is appropriate: The solution, cooled to 5° C - 8° C, is perfused into the coronary arteries by hydrostatic pressure of 100 mmHg (equivalent to initial height of perfusion bottle above level of heart = 140 cm). After cardiac arrest has ensued (within the first minute after starting perfusion) the perfusion bottle should be lowered to about 50-70 cm above the level of the heart, equivalent to 40-50 mmHg. In patients with pronounced coronary stenosis, a higher perfusion pressure (about 50 mmHg) will be necessary for a somewhat longer time. The overall perfusion time should be 6-8 minutes, so as to ensure homogeneous equilibration. Even for small hearts, a perfusion rate of 1 ml/min./gram-estimated-heart-weight at a perfusion pressure of 40-50 mmHg and a perfusion time of 6-8 min. should be enough to ensure equilibration. The heart may then be excised. The heart should tolerate a cold ischemic time of up to four hours.

Transport of a Donor Organ

The transport of a donor organ to the recipient utilizes a sterile pouch accomodating the size of the organ in an ice cold CUSTODIOL® solution. The organ must be completely covered by the solution.The pouch is sealed with adhesive tape and is placed into a second container which is also filled with CUSTODIOL® solution in order to prevent a breakdown of insulation and cooling by trapped air. The double-bagged organ is placed

into a sterile plastic container and closed with a secure lid. The plastic bag is then placed into a transport container packed with ice for transport. Information about the donor, copies of the laboratory results and blood samples from the donor are also included. The transport of the donor organ in CUSTODIOL® solution must be accomplished as quickly as possible.

Clinical Experience

Kidney Transplant Trials

A major multi-center prospective randomized clinical trail has been carried out in Europe comparing three perfusion and preservation solutions for use in kidney transplants.[1] The three solutions were the CUSTODIOL® HTK solution, the Belzer UW solution, and the Euro-Collins (EC) solution. Forty-seven centers participated and followed a strict protocol. Over a thousend kidneys were included in the study. In the HTK-UW study, there were 342 donors and 611 transplants (the UW group had 168 donors an 297 transplants, the HTK group had 174 donorsand 314 transplants). In the HTK-EC study, there were 317 donors and 569 transplants (the EC group had 155 donors und 277 transplants, the HTK group had 162 donors and 292 transplants).

This study directly compared kidney survival in the HTK group with the UW group, and also with the EC solution, and showed that for kidney transplants, the HTK solution performs as well overall as the UW solution, and significantly better than EC solution for initial nonfunction. The average cold ischemia time in the HTK-UW study was 25.8 hours in the HTK group and 25.5 hours in the UW group. In the HTK-EC group, the average cold ischemia time was 24.1 hours in the HTK group and 24.2 hours in the EC group. The overall kidney survival rates from the 47-center study for HTK versus UW, and HTK versus EC at four time points were:

	HTK	UW	HTK	EC
1 Month	91%	91%	85%	86%
12 Months	83%	82%	80%	74%
24 Months	77%	74%	76%	71%
36 Months	74%	68%	70%	67%

Delayed graft function that required two or more dialysis sessions during the first week was 20% (107/544) in the pooled HTK groups, 25% (66/266) for the UW group, and 32% (85/268) for the EC group. Initial nonfunction (INF) occurred in 33% of the kidneys in both HTK and UW groups, and in the other study, INF occurred in 29% of the HTK group and 43% of the EC group.

Liver Transplant Trials

Several clinical studies have been reported that examined the performance of CUSTODIOL® HTK solution in liver transplants. These studies have collected data on survival rates and other outcome measures. The primary evidence for effectiveness has come from a four-center prospective clinical study carried out under the auspices of the Eurotransplant organization of Leiden, The Netherlands. The four centers were located at Essen, Innsbruck, Göttingen and Vienna. The result from this and other studies are discussed below.

Gubernatis summarized the experience at the Medizinische Hochschule Hanover, Clinic for Abdominal and Transplantation Surgery, for livers preserved in UW solution and in HTK solution. This was a retrospective study of transplants conducted at Hanover between 1988 and 1996. During this period there were 515 liver transplants using the UW solution and 232 using HTK solution. These transplants were carried out in 416 patients using UW and 197 using HTK (some were re-transplants). The survival curves for all patients out to five years were essentially indistinguishable and certainly not significantly different statistically. An update on the Hanover experience through 1999 showed that 461 livers had been preserved with HTK solution and 607 with UW solution. Prof. Gubernatis reiterated his earlier conclusion that the two solutions were equivalent in their ability to preserve the liver for transplant.

A randomized prospective study was organized under the direction of Prof. J. Erhard at Essen, comparing 30 livers preserved with HTK solution with 30 livers preserved with UW solution. There were two cases of initial nonfunction (INF) in the UW group and one case of INF in the HTK group. Graft survival at 3 months was 87 % in the HTK group and 80% in the UW group (p=0.21). Patient survival at 30 months was 77% in the HTK group and 74% in the UW group.
A multi-center prospective clinical study was carried out in Europe to evaluate the performance of the HTK solution in liver transplants[2]. Four transplant centers participated. 228 livers were included in the study (205 were initial translants, 23 were re-transplants). This trial took place during 1996-1999 under the auspices of Eurotransplant. The four transplant centers participating were: Innsbruck Transplant Center; Vienna Transplant Center; University Clinic, Essen; and University Hospital, Göttingen. The (patient) survival rate at one year

[1]de Boer J, De Meester J, Smits JMA, Doxiadis IIN, Groenewoud AF, Persijn GG (1999). Eurotransplant randomized multicenter study comparing kidney graft preservation with HTK, UW, and EC. *Transplantation* in press, publication about December 1999.

[2] Pokorny H, Grünberger T, Rockenschaub S, Windhager T, Rosensting A, Lange R, et al (2000). Preservation of the liver with HTK--a multicenter experience. Poster presented at International Congress of the Transplant Society, Rome, Italy.

observed in this study was 82.5%. The following table shows the patient survival at different times in the direct comparison study at Essen, the four-center prospective study, and the Hanover retrospective study. These data show that the patient survival rates for HTK-preserved livers are similar to those for UW-preserved livers.

	HTK-Ess	UW-Ess	HTK (4-Ctr)	HTK-Han	UW-Han
1 Month	87 %*	80 %*			
3 Months			82,5 %		
12 Months				71%	72%
30 Months	77 %	74 %		69%	67%

*Graft survival

Pancreas Transplant Trials

In *Transplantation*,[3] Fridell, et al. reported a clinical study at Indiana University School of Medicine of pancreas transplantation where HTK and UW solutions were compared. On May 1, 2003, the transplant center switched from UW solution to HTK solution, and the last ten consecutive UW-preserved pancreata were compared to the first ten consecutive pancreata preserved with HTK. The study found no differences between the two solutions in early graft function or graft survival. All 20 patients and pancreata were well at 30 days. All parameters of graft function were equivalent during the first week, at 14 days, and at 30 days. The authors conclude that "Within this range of cold ischemia time [11 ± 4 hrs], UW and HTK demonstrate similar efficacy in pancreas preservation".

A retrospective study of 33 pancreas transplants during the period September 2002 and October 2003 was carried out at the University of Pittsburgh, Thomas E. Starzl Transplantation Institute.[4] Seventheen of the pancreata were preserved with UW solution and 16 were preserved with HTK. The cases were analyzed for initial graft function and complications in the first 30 days. There were no significant differences in donor characteristics between the two groups, except for donor age, 21.9 in the HTK group and 29.5 in the UW group, a difference that was statistically significant, but not clinically meaningful.

All patients were alive at 30 days, but one pancreas in the HTK group failed due to a donor-derived infection (the patient was successfully retransplanted). One-year graft survival were similar in the two groups. Markers of graft function were measured at day 1 and day 10. There were no significant differences except that at day 10, serum creatinine levels averaged 2.42 ± 0.48 mg/dL in the HTK group and 1.77 ± 0.46 mg/dL in the UW group, a result that was statistically significant. The experience in the first 100 pancreas transplants using HTK had shown comparable complication rates, serum creatinine, and graft survival, compared to their historical experience with UW.

A study of 100 pancreas transplants at Chirurgische Klinik, Ruhr-Universität was reported by Riege, et al.[5] In 95 cases, UW solution was used and in five cases, HTK was used. All 100 transplants required initial insulin administration. In the HTK group, there were zero instances of primary non-function, vascular thrombosis, and hemodialysis, along with one case of graft pancreatitis. The comparable numbers in the much larger UW group were 0, 7, 1 and 3. Patient survival at one year was 93 % in the combined groups, while graft survival was about 75 % (differential rates were not reported).

Becker, et al.[6] reported on the experience of 16 simultaneous kidney-pancreas transplants at Medizinischen Hochschule Hannover during 1999-2001, all using HTK as cold storage solution. One pancreas graft failed due to thrombosis and one kidney-pancreas graft failed due to acute rejection, so the one-year pancreas graft survival was 87 % and the kidney survival was 93 %. All of the patients were alive at one year. Initial non-function was seen on one pancreas and initial dysfunction in one patient. There were four episodes of rejection.

[3]Fridell JA, Agarwal A, Milgrom ML, Goggins WC, Murdock P, Prescovita MD (2004). Comparison of Histidine-Tryptophan-Ketoglutarate solution and University of Wisconsin solution for organ preservation in clinical pancreas transplantation. *Transplantation,* **77**: 1304-1306.

[4]Potdar S, Malek S, Eghtesad B, Shapiro R, Basu A, Patel K, Broznick B, Fung J (2004). Initial experience using histidine-tryptophan-ketoglutarate solution in clinical pancreas transplantation. *Clinical Transplantation,* **18**: 661-665

[5]Riege R, Büsing M, Kozuschek (1999). Preservation of the pancreas for transplantation. *Transplant Proceedings,* **31**:2095-2096

[6]Becker T, Lück R, Lehner F, Höppner J, Bektas H, Nashan B, Klempnauer J (2001). Use of HTK perfusion solution in pancreas-kidney transplantation. Acta Chir Austriaca, **33** (Suppl to No. 174): 1-1.

Heart Transplant Trials

Several clinical studies have been reported that examined the performence of CUSTODIOL® HTK Solution in heart transplants. These studies have collected data on survival rates and other outcome measures.

At the Bad Oeynhausen transplant center, during the period 1989-2002, 1233 hearts were preserved with the HTK Solution. 19 hearts were preserved with other solutions. The data reported here represent the entire experience of the center, with no cases excluded. The following table summarizes the experience at Bad Oeynhausen:

The Bad Oeynhausen Experience in Cardiac Transplantation

	HTK-Solution	Other Solutions*
Number of Subjects	1233	19
Age of Donor		
Median	33.8	36.2
Minimum	0	16
Maximum	72	65
Donor Cause of Death		
Traumatic Bleeding	501	6
Spontaneous Bleeding	491	9
Hypoxia	97	2
Gun Shot Wound	33	1
Domino	1	1
Cerebral Ischemia	43	
Brain Tumor	31	
Intoxication	18	
Other	18	
Cold Ischemia Time		
Median	194.6	213.1
Standard Deviation	42.3	43.1
Minimum	68	108
Maximum	340	289
Recipient Gender		
Male	1014 (82.2 %)	17 (89.5 %)
Female	219 (17.8 %)	2 (10.5 %)
Recipient Age		
Median	50.4	53.9
Standard Deviation	17.0	13.3
Maximum	77.9	66.4
Minimum	0	15.5
Recipient Diagnosis		
Cardiomyopathy	625	8
Coronary Artery Disease	479	9
Valve Disease	65	1
Congenital Disease	37	
Retransplant	21	1
Acute Myocarditis	2	
Other Diseases	4	

Causes of Death Post-TX		
Graft Rejection	52	1
MOF	25	
Graft Vasculopathy	3	
Acute Bleeding	1	
Infection	49	2
Acute left ventricular failure	11	
Right Ventriculare Failure	13	
Neurological Complications	13	2
Pulmonary Complications	3	
Abdominal Complications	6	
Perioperative Complications	8	
Primary Graft Failure	23 (1.9 %)	0
Deaths in First Year	248 (21 %)	7 (37 %)
Deaths in First Three Months	184 (16 %)	5 (27 %)

*The other solutions included UW, Roe, Ringer's lactate, normal saline, Plasmalyte A, Plegisol, Carmichael's and Stanford.

Wieselthaler et al[7]. reported a randomized prospective study conducted at the University of Vienna comparing CUSTODIOL® solution to Celsior, another cardiac cold storage solution. 48 patients were randomized to either the CUSTODIOL® group or the Celsior group. Following are the result from this study:

[7]Wieselthaler GM, Chevtchik O, Konetschny, Moidl R, Mllinger E, Mares P, Griessmacher A, Grimm M, Wolner E, Laufer G (1999). Improved graft function using a new myocardial preservation solution: Celsior. Preliminary data from a randomized prospective study. *Transplantation Proceedings,* **31**: 2067-2070

	HTK	Celsior
Number of Subjects	24	24
Perioperative Graft Failure	2/24 (8.3 %)	2/24 (8.3 %)
Patient Survival at 30 Days	22/24 (91.7 %)	23/24 (95.8 %)
Graft Survival at 30 Days	22/25 (88.0 %)	23/25 (92.0 %)
Spontaneous Stable Cardiac Rhythm Immediately after Opening Aortic Cross-Clamp*	9/24 (37.5 %)	19/24 (79.2 %)
Cold Ischemia Time (min.)		
Mean	199	183
Standard Deviation	54	43
Minimum	96	165
Maximum	290	282
Donor Age (Yrs)		
Mean	38	38
Standard Deviation	12	11
Recipient Age (Yrs)		
Mean	55	57
Standard Deviation	9	11
Donor Heart Dysfunction	7/24	2/24
Causes of First Graft Failure		
Infection		1
Acute Graft Failure	2	1
Deaths in Retransplanted Patients	1/1	0/1

* In the study reported by Wieselthaler et al., only 9/24 of CUSTODIOL®-preserved hearts returned immediately to normal sinus rythm, following reperfusion, compared to 19/24 in the Celsior-preserved hearts. However, in the larger study by Reichenspurner et al., 87 % of 137 CUSTODIOL®-preserved hearts returned immediately to normal sinus rhythm. It is not clear why these two studies showed such different results, though it may have been partly due do the larger numbers of cases of donor heart dysfunction in the HTK group.

A clinical trial of Celsior solution was carried out during the 13-month period May 1997 through May 1998, and was reported by Vega et al.[8] The data from Bad Oeynhausen (discussed above) during this same 13-month period was reanalyzed separately from the larger population for purposes of comparison with Celsior. 79 patients were transplanted during the period at Bad Oeynhausen and the 7- and 30-days survival values for Celsior and the control solutions from the Vega study, along with the data from the same period from Bad Oeynhausen, are shown in the following table. It should be noted that the Bad Oeynhausen center accepts some donor hearts that would normally be rejected by other centers. The data are presented both with and without so-called "critical" donor hearts (e.g., those with cold ischemia time above 240 min, donor age greater than 50 years, etc.). Without the "critical" cases, the acceptance criteria for the Celsior study and the Bad Oeynhausen non-critical cases are more similar.

Group	7-Day Survival	30-Day Survival
Data from Celsior study - Celsior preserved hearts	62/64 (96.9 %)	60/64 (93.7 %)
Data from Celsior study - Control* preserved hearts	63/67 (94.0 %)	59/67 (88.1 %)
Data from same 13-month period from Bad Oeynhausen for HTK, all patients included (n = 79)	75/79 (94.9 %)	70/79 (88.6 %)
Data from same 13-month period from Bad Oeynhausen for HTK, noncritical donors included (n = 51)	50/51 (98.0 %)	47/51 (92.2 %)

* The "control group" in the Vega study consisted of the pooled data from several different preservation solutions - whatever the center happened to use prior to the study. The solutions included UW, Roe, Ringer's lactate, normal saline, Plasmalyte A, Plegisol, Carmichael's, Stanford, and others.

Adverse Events Observed in the Clinical Studies

Kidney Studies

There were no unexpected adverse events in these clinical studies.The adverse events that occurred were expected because of the nature of transplantation. None are believed to be affected by any of the solutions.

Kidney failure rates in the first 48 hours were comparable in all groups: UW-15/297 and HTK-18/314; EC-15/277 and HTK-13/272.

In the HTK-UW kidney study, acute rejection episodes occurred in 99/314 (32%) in the HTK group and 105/297 (35%) in the UW group. In the HTK-EC study, acute rejection episodes occurred in 99/292 (34%) in the HTK group and 108/277 (39%) in the EC group.

Liver Studies

There were no unexpected adverse events in these clinical studies. The adverse events that occured were expected because of the nature of transplantation.

In the multi-center trial, primary dysfunction rate (PDF) was 10.3%, with the primary nonfunction rate (PNF) of 3.6%. Bile duct complications were seen in 19% of transplants. This compares with data from Eurotransplant on the UW solution: PDR of 15.2% and PNR of 7.8%.

Pancreas Studies

There were no unexpected adverse events in these clinical studies. The adverse events that occured were expected because of the nature of transplantation.

[8]Vega JD, Ochsner JL, Valluvan J, McGiffin DC, McCurry KR, et al. (2001). A multicenter randomized, controlled trial of Celsior for flush and hypothermic storage of cardiac allografts. *Ann. Thorac. Surg,* **71**: 1442-1447.

In the clinical study at the University of Indiana, there were no differences in initial graft function or graft or patient survival at 30 days.

In the clinical study at the University of Pittsburgh, one out of the 17 pancreata failed due to a donor-derived infection (the patient was successfully retransplanted). Markers of graft function were measured at day 1 and day 10. There were no significant differences except that at day 10, serum creatinine levels averaged 2.42 ± 0.48 mg/dL in the HTK group and 1.77 ± 0.46 mg/dL in the UW group, a result that was statistically significant. However, after 100 transplants using HTK at this center, the serum creatinine was not significantly different from levels that had been seen using UW.

Becker, et al.[9] reported on the experience at Medizinischen Hochschule Hannover of 16 simultaneous kidney-pancreas transplants during 1999-2001, all using HTK as cold storage solution. One pancreas graft failed due to thrombosis and one kidney-pancreas graft failed due to acute rejection, so the one-year pancreas graft survival was 87 % and the kidney graft survival was 93 %. All of the patients were alive at one year. Initial non-function was seen on one pancreas and initial dysfunction in one patient. There were four episodes of rejection.

Heart Studies

There were no unexpected adverse events in these clinical studies. The adverse events that occurred were expected because of the nature of heart transplantation.

In the Bad Oeynhausen experience, the primary dysfunction rate (PNF) was 1.9 %.

How Supplied

Bottles of	500 ml
Bottles of	1000 ml
Bags of	1000 ml
Bags of	2000 ml
Bags of	5000 ml

Store at 35,6°F - 46,4°F and protect from light.

Registration # : K 992209
: K 020924
: K 032794
: K 043461
: K 192408

[9]Becker T, Lück R, Lehner F, Höppner J, Bektas H, Nashan B, Klempnauer J (2001). Use of HTK perfusion solution in pancreas-kidney transplantation. Acta Chir Austriaca, **33** (Suppl to No. 174): 1-1.

Notice

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