

Pharmacists' guide to the management of organ donors after brain death

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Purpose. This article reviews organ donor pathophysiology as it relates to medication use with the goal of maximizing the successful procurement and transplantation of donor organs.

Summary. The number of patients requiring organ transplantation continues to grow, yet organ donation rates remain flat, making it critical to appropriately manage each organ donor in order to ensure viability of all transplantable organs. The care given to one organ donor is tantamount to the care of several transplant recipients. Aggressive donor management ensures that the largest number of organs can be successfully procured and improves the organs' overall quality. Hospital pharmacists are responsible for processing orders and preparing the medications outlined in donor management algorithms developed by their respective medical systems. It is important that pharmacists understand the details of the medications used in these protocols in order to critically evaluate each medication order and appropriately manage the donor. Typical medications used in organ donors after brain death include medications for blood pressure management and fluid resuscitation, medications necessary for electrolyte management, blood products, vasopressors, hormone replacement therapy, anti-infectives, anticoagulants, paralytics, and organ preservation solutions.

Conclusion. It is essential to provide optimal pharmacotherapy for each organ donor to ensure organ recovery and donation. Typical medications used in organ donors include agents for blood pressure management and fluid resuscitation, medications necessary for electrolyte management, blood products, vasopressors, hormone replacement therapy, anti-infectives, anticoagulants, paralytics, and organ preservation solutions.

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Solid organ transplantation remains a vital area of healthcare, with over 24,000 transplants performed in 2014 alone.¹ As of August 2016, approximately 120,000 patients were in need of a lifesaving organ. Every 10 minutes, 1 person is added to the list of those needing a transplant, while 21 people die each day waiting for a transplant.¹ The number of patients on this list continues to grow, yet organ donation rates remain flat.¹ Thus, it is critical to appropriately manage each potential organ donor in order to ensure optimal functioning of the donated organ and the viability of all transplantable organs.

Donor evaluation begins when the local organ procurement organization (OPO) is contacted. A member of the OPO will explain the procurement process to the family, obtain consent, coordinate evaluation of the donor, and communicate with the United Network for Organ Sharing (UNOS) to aid in matching the donor to appropriate recipients. A critical pathway for the organ donor has been developed that outlines the phases of organ donation, including referral, declaration of brain death and consent, donor evaluation, and donor management or recovery.² The pathway also provides guidance to providers regarding

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appropriate laboratory tests, diagnostics, respiratory care, treatments, medications, and outcomes in each phase of donation.

The care of potential organ donors differs from that of other critically ill patients. At the end of life, organ donors are frequently medically unstable, and this instability increases as the length of time between declaration of brain death and organ procurement grows.³ Timely management of the donor is imperative in order to minimize the occurrence of somatic death and increase the number of organs that can be successfully procured and transplanted. Management must balance the need to preserve multiple organs. Treatment that improves the function of one organ may be harmful to that of another organ. For example, the renal transplant team may want to optimize renal perfusion with fluids and diuretics, while the lung transplant team may want to avoid excessive hydration and the risk of fluid overload and pulmonary edema.

The Organ Procurement and Transplantation Network (OPTN) has issued policies that govern all transplant hospitals and organizations in the United States.⁴ While these policies are extensive and detail many aspects of organ transplantation, they are broad in their overall scope and do not provide specific details regarding medication use in and management of the organ donor. As such, the policies serve as guidelines by which OPOs practice and develop organization-specific algorithms to manage potential organ donors. Currently, no document exists that describes the unique pathophysiology of the donor, how this pathophysiology affects medication use, or the details of drug therapy management in this patient population.

Hospital pharmacists are responsible for processing orders and preparing the medications outlined in donor management algorithms developed by their respective medical systems. It is important that pharmacists understand the medications used in these

KEY POINTS

- Aggressive donor management ensures that the largest number of organs can be successfully procured and improves the organs' overall quality.
- Typical medications administered to organ donors after brain death include medications for blood pressure management and fluid resuscitation, medications necessary for electrolyte management, blood products, vasopressors, hormone replacement therapy, anti-infectives, anticoagulants, paralytics, and organ preservation solutions.
- It is important that hospital pharmacists understand the medications used in organ donor management protocols in order to critically evaluate each medication order and appropriately manage the donor.

protocols in order to critically evaluate each medication order and appropriately manage the donor. This article briefly reviews organ donor pathophysiology as it relates to medication use with the goal of maximizing the successful procurement and transplantation of donor organs.

Determination of death

After a deceased person is identified as a potential organ donor, an OPO is typically contacted by the primary team to determine the suitability of organ donation.³ Donors undergo standardized treatment algorithms to maintain organ perfusion. The basic goal is to maintain the hemodynamic stability and function of transplantable organs.⁵ Organ donors undergo an evaluation by an OPO in which the criteria for death will be assessed. Donors are evaluated based on neurolog-

ic criteria (brain death) or circulatory-respiratory criteria (cardiac death). The determination of death using either criterion may differ among institutions; however, a consensus statement released in 2015 outlines clear recommendations for making this determination.^{6,7} We refer the reader to either the consensus statement^{6,7} or UNOS guidelines for a more comprehensive review.²

Neurologic determination of death. A donor may experience complete loss of neurologic function due to traumatic or anoxic brain injury. A donor with complete loss of neurologic function will exhibit many signs of brain injury, including nonreactive pupils, absence of gag reflex, and apnea. Once the provider concludes that medical management is futile, the focus changes from maintaining cerebral perfusion to managing the donor for organ procurement.⁶ This includes maintaining hemodynamic stability and organ perfusion.

Circulatory determination of death. Organ donation after circulatory determination of death has increased in frequency due to the increased need for organs. The process is different from that of organ donation after neurologic death. Donors in this category must have permanent circulatory arrest (observed for a minimum of two minutes) before declaration of death and the initiation of organ transplantation.^{6,8}

The information in this article applies to the management of donors after brain death, unless otherwise specified.

Blood pressure management and fluid resuscitation

Donors may experience hemodynamic instability as a result of hormonal, neurohormonal, and pro-inflammatory responses after brain death.⁶ Brain death occurs in two phases: progressive ischemia and brainstem death. After a neurologic insult, intracranial pressure elevates, leading to high mean arterial pressure and subsequent cerebral edema and

ischemia. Ischemia within the pons results in a phenomenon known as the Cushing reflex. Cushing reflex is a result of sympathetic stimulation leading to hypertension, bradycardia, and irregular breathing. Once ischemia reaches the medulla, sympathetic stimulation and autonomic storm occur in an effort to maintain cerebral perfusion. Autonomic storm is characterized by a significant increase in circulatory dopamine, norepinephrine, and epinephrine and leads to severe vasoconstriction. In addition to sudden hypertension (systolic blood pressure of >200 mm Hg), tachycardia (heart rate exceeding 140 beats/min), and, potentially, arrhythmias, catecholamine-induced vasoconstriction will increase myocardial oxygen demand, creating a discordance of oxygen supply and demand. Subendocardial ischemia may occur during this phase. Catecholamines can also directly affect the myocardium, resulting in myocyte injury and ventricular dysfunction.^{6,9,10}

In the final stage of brain death, complete ischemia of the brainstem and spinal cord coincides with herniation and leads to total loss of sympathetic tone, cardiac stimulation, and circulating catecholamines. This phase is characterized by profound vasodilation leading to hypotension and hemodynamic instability as well as cardiac conduction abnormalities and arrhythmias. Additional factors that may affect hemodynamic stability in a donor include diabetes insipidus attributable to ischemia progressing to the pituitary, sepsis resulting in inflammation and capillary leakage, metabolic acidosis, and pulmonary edema.^{6,9}

Hemodynamic instability may lead to reduced oxygen supply and ischemia in the donated organ. Proper management of donor hemodynamics is crucial to avoid dysfunction of the organs planned for donation.⁵ Short-acting i.v. antihypertensives have been used to control hypertension during autonomic storm. By controlling hypertension during autonomic storm with

antihypertensives, preservation of left ventricular function and increased viability of cardiac grafts have been found when compared with no treatment of autonomic storm hypertension.¹⁰ The preferred antihypertensive agent has not been established. Agents used include nicardipine, a short-acting dihydropyridine calcium channel blocker; and esmolol, a short acting β -1 selective blocker. Theoretically, esmolol may be the preferred agent due to its ability to attenuate adrenergic stimulation.¹⁰ The use of short-acting agents is preferred due to the short period of autonomic storm during brain death.¹⁰ Dosing of esmolol for autonomic storm is not standardized. Esmolol has a half-life of approximately 9 minutes and a duration of action of 20–30 minutes. Esmolol for hypertension is typically initiated with a bolus dose of 100–500 μ g/kg followed by an infusion of 150 μ g/kg/min, if needed.¹¹ Hypotension should be avoided, and the donor should be closely monitored due to the unpredictable duration of autonomic storm.

The profound vasodilation after autonomic storm can be very difficult to manage. Hemodynamic goals for the potential donor include maintaining a mean arterial pressure of >60 mm Hg, central venous pressure of 6–10 mm Hg, urine output of 1–3 mL/kg/hr, and cardiac index of >2.4 L/min to avoid end-organ damage and ischemia.³ Intravascular volume

should be replenished before initiating vasopressor therapy in an attempt to correct hypovolemia. The donor's fluid status should be assessed to determine the need for fluid resuscitation or maintenance. Volume deficits should be corrected with fluid boluses of 1–2 L of isotonic 0.9% sodium chloride injection administered as rapidly as possible. Typical maintenance fluids include dextrose, isotonic or half-isotonic 0.9% sodium chloride injection, and electrolytes administered at 30–50 mL/hr (Table 1).¹² Serum sodium, potassium, and glucose concentrations should be assessed when choosing the type of fluid to administer (Table 2).¹³ Sodium bicarbonate (50–150 mmol/L) may be added to fluids in donors with metabolic acidosis. For donors with hypernatremia, 0.45% sodium chloride injection may be administered. Studies addressing fluid choice are lacking.

Electrolytes

Several electrolyte imbalances may occur in the potential organ donor, including hypernatremia and acidosis (Table 2). Electrolyte imbalances may be due to the hyperglycemic state occurring after brain death.³ Hyperglycemia alters osmolality leading to shifts in electrolytes. According to the OPTN policies, electrolytes should be included in metabolic testing when evaluating organ donors. Imbalances have been connected to

Table 1. Typical Maintenance Fluids for Organ Donors After Brain Death¹²

Maintenance Fluid	Osmolarity, mOsm/L	Infused Volume, mL	Intravascular Volume Expansion, mL
Crystalloids			
0.9% Sodium chloride injection	287	1000	250
5% Dextrose injection	278	1000	100
Colloids			
Albumin 5%	~280	500	500
Albumin 25%	~280	100	500
Hetastarch 6%	310	500	500

Table 2. Electrolyte Goals for Organ Donors After Brain Death^{6,9,13}

Electrolyte	Goal Concentration	Serum Concentration Before Replacement Therapy	Dose to Administer	Maximum Rate of Administration
Sodium	135–150 meq/dL	Serum osmolality and volume status should be assessed before initiating replacement therapy	... ^a	... ^a
Potassium ^b	4–6 meq/L	2.5–3.4 meq/L <2.5 meq/L	20–40 meq i.v. 40–80 meq i.v.	40 meq/hr
Magnesium ^b	1.7–2.3 mg/dL	1–1.5 mg/dL <1 mg/dL	Magnesium sulfate 1–4 g Magnesium sulfate 4–8 g	Magnesium sulfate 1 g/hr
Calcium (ionized)	>1.1 mmol/L	<0.9 mmol/L	Calcium gluconate 3 g or calcium chloride 1 g	May be given over 10 min if symptomatic (tetany, CNS and cardiovascular symptoms)
Phosphorus ^{b,c}	3–4.5 mg/dL	2.3–2.7 mg/dL 1.5–2.2 mg/dL <1.5 mg/dL	0.08–0.16 mmol/kg 0.16–0.32 mmol/kg 0.32–0.64 mmol/kg	Phosphate 7 mmol/hr

^aManagement of sodium disorders is complex and beyond the scope of this article. CNS = central nervous system.

^bPatients with renal insufficiency should receive 50% of the normal dose.

^cReplacement dose based on phosphate component. May be given as sodium phosphate or potassium phosphate.

poor outcomes, such as graft loss after liver transplantation in patients with hypernatremia.³

These imbalances should be managed through electrolyte replacement and fluid management. Electrolyte goals are included in Table 2. Potassium should be replaced intravenously at a dose of 20–40 meq when the serum concentration is 2.5–3.4 meq/L. Higher doses (40–80 meq) should be used when the serum concentration is less than 2.5 meq/L. Potassium should be administered no faster than 40 meq/hr. Similarly, magnesium, calcium, and phosphorus are also replaced based on serum concentrations. For example, serum magnesium concentrations of <1 mg/dL should be replaced with 4–8 g magnesium sulfate, while serum concentrations of 1–1.5 mg/dL only require 1–4 g of magnesium sulfate. The rate of administration should be limited to 1 g/hr. Two different products may be used for calcium replacement: calcium gluconate and calcium chloride. The dosing differs for these agents, as calcium chloride contains three times

the amount of elemental calcium when compared with calcium gluconate. Regardless, calcium should be replaced when serum calcium concentrations drop below 0.9 mmol/L with either 3 g of calcium gluconate or 1 g of calcium chloride. Finally, phosphorus may be replaced with products containing either sodium phosphate or potassium phosphate. The provider should assess the electrolyte status of the donor when choosing a product. Replacement is weight based depending on the current serum phosphorus level and can be referenced in Table 2.

Colloids, blood products, and vasopressors

Colloids such as 5% albumin (12.5–25 g given as needed) and packed red blood cells (PRBCs) serve an additional purpose when used for hemodynamic stabilization. If the donor is requiring large amounts of crystalloids, colloids may be used to avoid fluid overload and tissue edema.^{2,14} In addition, PRBCs can be used to correct anemia to a goal hematocrit value above 30% to maintain adequate oxygen delivery.

The use of PRBCs also increases systemic vascular resistance.^{2,3}

Hydroxyethyl starch produces volume expansion by increasing the oncotic pressure within the intravascular space. Published literature guiding fluid resuscitation in organ donors studied 16 brain-dead multiorgan donors randomized to receive a combination of hydroxyethyl starch and electrolyte solution or crystalloid fluid therapy alone.¹⁵ Hemodynamic values were maintained in each group. A smaller infused volume was necessary in the group receiving hydroxyethyl starch plus electrolyte solution; however, hydroxyethyl starch increases the risk of acute kidney injury and the need for renal replacement therapy. This risk may translate to an increased risk of impairment in recipient renal function when the donor receives hydroxyethyl starch.^{12,16}

Once adequate fluid resuscitation has occurred, vasoactive drugs may be initiated for persistent hypotension. Pharmacologic properties should be taken into consideration before initiating therapy, as there is no current

Table 3. Vasopressors for Use in Organ Donors After Brain Death^{9,12}

Agent	Starting Dose	Target Receptors	Monitoring Required	Place in Therapy
Dopamine	3–10 µg/kg/min	3–5 µg/kg/min: dopamine 5–10 µg/kg/min: β ₁ 10–20 µg/kg/min: α ₁	Heart rate, blood pressure, electrocardiogram, renal function	Typically first line
Epinephrine	0.05–0.5 µg/kg/min	β ₁ , β ₂ , α ₁	Heart rate, blood pressure	Second line
Norepinephrine	0.1–2 µg/kg/min	β ₁ , α ₁	Heart rate, blood pressure	Second line
Phenylephrine	0.1–1 µg/kg/min	α ₁	Heart rate, blood pressure	Avoid as sole agent due to potent α-adrenergic effects
Isoproterenol	2–10 µg/min	β ₁ , β ₂	Heart rate, blood pressure, electrocardiogram, respiratory rate, serum glucose, potassium, magnesium	May be used for bradyarrhythmia due to vagus nerve disruption in brainstem (typically not responsive to atropine)
Vasopressin	0.03 units/min	V ₁	Heart rate, blood pressure, serum and urine sodium, fluid input and output	First line; may allow for dose de-escalation of other vasopressors

consensus on the ideal combination of vasopressors for this population (Table 3).³ Dopamine is typically the vasopressor selected to manage organ donors with hemodynamic instability.³ Dopamine exerts its ability to protect endothelial cells via induction of protective enzymes, which is thought to lead to beneficial outcomes in organ recipients.^{17,18} One randomized controlled trial studied the use of dopamine as pretreatment versus placebo in 300 brain-dead donors to identify the impact of pretreatment on early graft function after renal transplantation.¹⁷ Dopamine was initiated at 4 µg/kg/min and continued through cross-clamp of the aorta during procurement. The investigators found pretreatment with dopamine reduced the need for dialysis after kidney transplantation. If hemodynamic support is needed beyond dopamine 10 µg/kg/min, another vasoactive drug should be added, preferably one that does not exert primary α-adrenergic vasoconstrictor effects.⁶ Excessive α-adrenergic stimulation may lead to pulmonary edema by increasing pulmonary capillary permeability.⁶ Dopamine may not

be an ideal agent to use in donors with uncorrected tachyarrhythmias.

Vasopressin is used as an alternative to dopamine for first-line therapy for managing hemodynamic instability because it augments catecholamine stimulation, triggers peripheral vasoconstriction, and treats diabetes insipidus.^{3,6} Its role in diabetes insipidus and hemodynamic stability has been reviewed extensively in hormonal therapy.

Norepinephrine has also been used as an option for blood pressure support in donor management. Data are conflicting regarding the impact on recipient survival after norepinephrine use in donors.^{19,20} In heart transplant recipients, a retrospective study found no difference in recipient survival during follow-up when donors were pretreated with either norepinephrine or dopamine. However, a subgroup analysis of patients who were followed for five years revealed that norepinephrine pretreatment improved long-term survival.¹⁹

Hormone replacement therapy

When aggressive volume reple-

tion and the use of vasopressors do not achieve adequate hemodynamic stability, the use of hormone replacement is often considered. Data support the theory that in brain death, malfunction of the hypothalamic–pituitary–adrenal axis results in low levels of cortisol and thyroid hormones, which can contribute to hypotension and subsequent organ deterioration. The administration of exogenous hormones has been found to increase hemodynamic stability, decrease requirements for vasoactive therapy, and increase the total number of organs transplanted.³

Currently, exogenous hormone therapy can include the administration of four separate hormones: thyroid hormone (triiodothyronine or thyroxine), corticosteroids, antidiuretic hormone (vasopressin or desmopressin), and insulin. These can be given alone or in combination with each other, though the optimal regimen of these hormones remains unknown.²¹

Decreased circulating levels of thyroid hormones have been observed in donors after brain death. Low levels of

triiodothyronine and thyroxine may contribute to hemodynamic instability in these donors by causing a decrease in available adenosine triphosphate, reduced myocardial energy stores, and a transition from aerobic to anaerobic metabolism.²² In order to avoid these negative effects, UNOS recommends the use of triiodothyronine in the management of cardiothoracic donors.²³ Triiodothyronine has a shorter half-life than thyroxine and is more potent and thus preferred for donor management.²⁴ Liothyronine sodium (the sodium salt of the L-isomer of 3,3',5-triiodothyronine [(l-triiodothyronine)]) can be administered intravenously as a 4- μ g (of liothyronine) bolus injection, followed by a 3- μ g/hr continuous infusion.¹² The use of i.v. levothyroxine (sodium salt of the L-isomer of thyroxine [thyroxine]) may also be effective, as it is converted into active triiodothyronine in the body. However, this conversion process may occur within several hours of administration, which could delay the cardiac effects.²⁵ Levothyroxine sodium can be administered as a 20- μ g bolus injection followed by a continuous infusion of 10 μ g/hr. This can be adjusted to maintain a systolic blood pressure of >100 mm Hg. Adverse effects include tachycardia, tremors, fever, and arrhythmias.

A retrospective review of 63,593 brain-dead donors evaluated the use of triiodothyronine/thyroxine administration and posttransplantation organ graft survival in the recipients at 1 and 12 months. In study 1, full documentation of triiodothyronine/thyroxine administration was available, but information regarding corticosteroids, antidiuretic hormone, and insulin were not fully recorded. In study 2, full documentation of the administration of all four hormones was available. In study 1, triiodothyronine/thyroxine therapy led to a mean of 3.35 organs donated per donor, while no therapy led to a mean of 2.97 organs per donor. In study 2, triiodothyronine/thyroxine therapy

led to a mean of 3.31 organs per donor, while no therapy led to 2.87 organs per donor. Overall, therapy with triiodothyronine/thyroxine was associated with the procurement of significantly more hearts, lungs, kidneys, pancreases, and intestines, but no significant difference in the number of livers procured was found. In addition, donor therapy with triiodothyronine/thyroxine was associated with improved posttransplantation graft survival or no difference in survival, except for pancreas recipient survival at 12 months in one study group.²⁶ However, despite the positive outcomes of some studies, additional studies have found mixed results, and a beneficial effect on hemodynamic status has not been proven.²⁷⁻³⁰ Randomized, prospective trials are needed to determine the influence of triiodothyronine/thyroxine therapy in donor management.

The dysfunction of the hypothalamic-pituitary-adrenal axis also leads to depletion of antidiuretic hormone and can cause central diabetes insipidus in up to 90% of brain-dead donors. Dehydration, hemodynamic instability, and hypernatremia have been described in untreated donors. Vasopressin, an exogenous form of antidiuretic hormone, is used to prevent or control polyuria, polydipsia, and dehydration in donors with central diabetes insipidus. The use of vasopressin to replete levels of circulating antidiuretic hormone has been shown to improve the probability of organ transplantation in kidney, heart, liver, lung, and pancreas donors.²⁵ It may also help contribute to improved hemodynamic stability and enhance the donor's response to catecholamines.³¹ In donors with diabetes insipidus who are at high risk of developing hypovolemia or continue to be hypotensive despite crystalloid repletion, vasopressin can be initiated with a bolus of 1 unit followed by a continuous infusion of 0.5–4 units/hr. Because of its potent effects on vasoconstriction, vasopressin can decrease renal blood flow, which may lead to ischemic injury of the donor kidneys.³²

Desmopressin, a synthetic vasopressin analog, has a longer duration of action and a decreased vasoconstrictor effect compared with vasopressin. Desmopressin can be given at a rate of 0.5–2.0 μ g/hr every two to three hours adjusted to achieve a urine output goal of 1–3 mL/kg/hr. Guesde and colleagues³² assessed the effects of desmopressin in brain-dead donors on both early and long-term graft function in kidney transplant recipients. Patients were randomized to receive either desmopressin as a 1- μ g i.v. bolus injection every two hours when urine output exceeded 300 mL/hr or no desmopressin. Kidney transplant recipients were assessed during the first two weeks after transplantation, as well as long-term. The administration of desmopressin decreased diuresis in donors and did not appear to influence serum creatinine concentration, the need for dialysis during the first two weeks after transplantation, or long-term survival of renal transplant recipients. Both vasopressin and desmopressin are known to control diuresis and decrease inotropic requirements.³²⁻³⁴ Retrospective database reviews have found that desmopressin and vasopressin can improve the number and quality of organs recovered from brain-dead donors.³⁵⁻³⁸

After the diagnosis of brain death, corticosteroids are administered to moderate the inflammatory response by inhibiting the release of proinflammatory cytokines and stabilizing cell membranes. The use of corticosteroids in organ donors has been associated with a decrease in early graft failure and rejection episodes in transplant recipients.^{23,39,40} Methylprednisolone may help to decrease pulmonary edema and stabilize lung function.⁴¹ However, the influence on recipient allograft outcomes remains controversial. One prospective study randomized 100 donors to receive methylprednisolone or control.⁴² Recipients of liver transplants from donors who received corticosteroids had a decreased rate of acute rejection within the first six months after trans-

plantation compared with the control group.

In a prospective multicenter cluster study ($n = 259$), brain-dead donors received either low-dose hydrocortisone or no corticosteroids (control group).⁴³ Norepinephrine weaning was improved in donors treated with low-dose hydrocortisone, but no significant difference in primary function recovery of transplanted allografts was found between groups. Similar results were seen in a trial of 50 donors who either received pretreatment with methylprednisolone or no pretreatment before organ harvesting.⁴⁴ Three-month kidney allograft survival times were similar between groups.

Dhar et al.⁴⁵ conducted a study of 132 consecutive brain-dead donors managed with either a high-dose (methylprednisolone 15 mg/kg) or a low-dose (300 mg hydrocortisone) corticosteroid regimen. The oxygenation rate of transplanted organs was similar in both groups, though insulin requirements and glycemic control were improved in the hydrocortisone group. The authors concluded that the low-dose corticosteroid regimen did not result in worsened donor pulmonary or cardiac function when comparable organs were transplanted in the group receiving methylprednisolone 15 mg/kg. According to both the Society of Critical Care Medicine (SCCM) consensus statement and the UNOS recommendations for cardiothoracic donors, methylprednisolone 15 mg/kg i.v. can be used to reduce the inflammatory cascade that occurs after brain death.^{2,6} The SCCM consensus statement also gives equal weight to methylprednisolone 1000 mg i.v. or a 250-mg bolus injection followed by an i.v. infusion at a rate of 100 mg/hr. No recommendation was made regarding the dosing of hydrocortisone in either guidance document.^{2,6}

Hyperglycemia is a common finding in brain-dead donors due to the physical stress of their injury, infusion of dextrose-containing solutions, changes in carbohydrate metabolism, and peripheral insulin resistance. This

hyperglycemia can damage the pancreatic β cells, which may lead to graft dysfunction in the pancreas transplant recipient.⁴ Intravenous insulin infusions administered at a minimum rate of 1 unit/hr adjusted to achieve goal blood glucose levels of 120–180 mg/dL may be used, especially in pancreas donors, to help minimize this risk.² In one study, prospective data were collected for organ donors after neurologic determination of death from UNOS (Region 5 from 2010 to 2012, $n = 1611$).⁴⁶ Hyperglycemia was associated with lower organ transplantation rates and worse graft outcomes. Targeting a glucose concentration of ≤ 180 mg/dL seems to preserve outcomes and is consistent with general critical care guidelines.

The use of concomitant hormone therapies has also been studied in organ donors after brain death. A retrospective, multivariate analysis of brain-dead donors ($n = 10,292$) revealed that hormone replacement (methylprednisolone i.v. bolus injection and infusions of vasopressin and either triiodothyronine or thyroxine) was associated with a significantly increased probability of an organ being transplanted from a donor.³⁰

Antiinfectives

The presence of an active infection can be detrimental to the organ recipient, and all organ donors should be screened for infectious processes.⁴⁷ Per OPTN policy, blood and urine cultures should be collected on all potential organ donors, and donors should be screened for multiple infectious risks including but not limited to human immunodeficiency virus, hepatitis, cytomegalovirus, Epstein-Barr virus, and syphilis.² Depending on the donated organ, additional tests may be required such as a sputum Gram's stain for potential lung donors.

Typically, donor organs are not used in the presence of gram-negative bacteremia or an invasive fungal infection.⁴⁷ However, antimicrobials may be used in the donor and the recipient to manage such infections in order to

salvage the organ and support better outcomes for the organ recipient. Infected donors should ideally receive antimicrobial therapy for at least 24–48 hours. Optimally, a clinical response to therapy (improved white blood cell count and improved hemodynamics) should also be demonstrated before procurement.

Antimicrobial selection should be guided by multiple factors, including active infectious diagnosis, length of stay, and risk factors for multidrug-resistant organisms (e.g., chronic dialysis, previous use of antibiotics, previous hospitalization).⁴⁸ Donors with these risk factors should receive treatment with a broad-spectrum antimicrobial such as piperacillin–tazobactam, vancomycin, cefepime, or meropenem. However, organ donors may not receive antimicrobials until the time of transplantation if no active infectious diagnosis is present at the time of death. Donors may receive prophylactic therapy such as cefazolin at the time of transplantation, according to ASHP's "Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery."⁴⁷ A detailed discussion of blood-borne infectious disease and prophylaxis is outside the scope of this article. Readers should refer to their local OPO for more information.

Heparin

One of the major factors affecting the survival of a donated organ is blood circulation to the organ after reperfusion. Thrombosis is a concern once circulation is temporarily lost during the organ procurement process.⁴⁹ Common practice includes administering heparin i.v. before aortic cross-clamping to avoid thrombotic complications.^{49,50}

Heparin acts as a potent anticoagulant by inactivating thrombin and activated factor X.⁵¹ While no standard dosing regimen currently exists, a heparin dose of 30,000–40,000 units i.v. administered after the declaration of brain death has been widely accepted.⁵⁰

Evidence regarding the use of thromboprophylaxis in organ donors is limited; however, the percentage of pulmonary emboli found during organ procurement is high, possibly due to the mechanism of donor injury.⁴⁹ Thus, it is reasonable to continue thromboprophylaxis to prevent the occurrence of pulmonary emboli. In some cases, donors may have heparin-induced thrombocytopenia (HIT), which precludes the use of heparin for thromboprophylaxis. If heparin were administered to an organ donor at the time of organ recovery, an acute thrombotic reaction could occur. While data assessing this issue in the organ donor population are limited, it is clear that thrombosis in the donated organ can result in potential early allograft dysfunction.

Argatroban (a direct thrombin inhibitor) may be used for prophylaxis and treatment of thrombosis in donors diagnosed with HIT. Bleeding is a complication of argatroban use, but the benefit of thrombosis prevention is thought to outweigh this risk. Two case studies have described the use of argatroban in multiorgan donors (liver, kidneys, and heart) after a confirmation of HIT.⁵² The donors received

argatroban 200 mg over 15 minutes before aortic cross-clamping. Organs were donated to seven recipients, and no thrombotic events or complications related to HIT were reported in organ recipients after transplantation.

Paralytics

Donors determined to be brain-dead are considered to have an irreversible loss of brain function. While this occurs, it is possible for the donor to continue to exhibit reflex movements due to the continued function of spinal reflexes.⁵³ Examples of reflex movements include periodic leg movement, raising of upper extremities, and triple flexion.

It is important that the donor not receive paralytic agents or sedatives before the determination of brain death in order to ensure an accurate neurologic assessment. However, once the diagnosis is confirmed, representatives from OPOs may request the use of paralytic agents to manage movements due to spinal reflexes. When monitoring the use of these agents in neuromuscular blockade, providers may use the train-of-four (TOF) method to determine the degree of paralysis. With this method, periph-

eral motor nerves are electrically stimulated with four sequential stimuli over a two-second period. Providers adjust the dose of the paralytic agent in response to the muscle innervated by the stimulated nerve. The number of muscle twitches, which can range from zero to four, is recorded. If the donor responds with four twitches, the paralytic dose may be increased. Alternatively, zero twitches may indicate the need to decrease the dose. An acceptable TOF goal in organ donors is one or two twitches.⁵⁴

No specific neuromuscular blocker has been identified as the preferred agent for use in organ donors after brain death; however, the donor's renal, hepatic, and cardiovascular statuses should be considered when selecting an agent (Table 4). Nondepolarizing neuromuscular blockers act by antagonizing the action of acetylcholine at the postsynaptic nicotinic receptor.⁵⁵ In contrast to depolarizing neuromuscular blockers, such as succinylcholine, nondepolarizing agents do not cause a change in the receptor but a gradual reduction in end-plate potential.⁵⁶

Rocuronium, vecuronium, and pancuronium may be preferred in

Table 4. Comparison of Neuromuscular Blockers Used in Organ Donors After Brain Death^{55,56}

Variable	Pancuronium	Vecuronium	Rocuronium	Atracurium	Cisatracurium
Loading dose ^a	0.08 mg/kg	0.1 mg/kg	0.6 mg/kg ^b	0.4 mg/kg	0.1 mg/kg
Maintenance dose	0.02–0.04 mg/kg/hr	0.02–0.04 mg/kg/hr	0.01–0.012 mg/kg/min	0.4 mg/kg/hr	2–10 µg/kg/min
Prolonged elimination in renal failure	Yes	Yes	Yes	No	No
Onset of action	2–3 min	3–5 min	1–2 min	2–3 min	2–3 min
Half-life	110 min	65–75 min	66–144 min	20 min	22–29 min
Prolonged elimination in hepatic failure	Yes	Yes	Yes	No	No
Adverse reactions	Tachycardia, hypotension	Bradycardia, flushing	Tachycardia, hypertension	Histamine release, flushing	Bradycardia, hypotension

^aBased on actual body weight unless otherwise noted.

^bMay use ideal body weight if patient is morbidly obese.

donors with normal renal and hepatic functions who are not receiving corticosteroids. Corticosteroids may be used after the diagnosis of brain death to moderate the inflammatory response. Adverse cardiovascular effects, such as hypotension, associated with neuromuscular blockers are related to stimulation or blockade of the autonomic nervous system and vasodilation due to histamine release. Anaphylaxis is extremely rare. Pancuronium may be the drug of choice in donors with normal renal and hepatic functions due to the low cost of the drug. However, the possibility of hypotension due to pancuronium-induced histamine release should be considered when choosing an agent. In donors with renal or hepatic insufficiency, atracurium or cisatracurium may be preferred because of the drugs' spontaneous degradation via Hofmann elimination.⁵⁵

Organ preservation solutions

Graft preservation remains one of the most important aspects of transplantation, as it determines graft survival and overall patient outcomes. Hypothermia is commonly used to decrease organ metabolic activity and cellular degradation during the ex vivo period; however, it may not prevent all cellular damage that can occur. Preservation solutions have been developed to be used in conjunction with hypothermia for additional cellular protection.

These solutions are commonly formulated with three general components: colloids, buffers, and antioxidants. Colloids are used to combat tissue edema by promoting water retention in the extravascular space, rather than moving into the graft cells and creating cellular edema. Buffers combat the negative effects of acidosis as the organ transitions from aerobic to anaerobic metabolism attributable to ischemia. Antioxidants are used to counteract the effects of reactive oxygen species created during ischemia, which can cause tissue damage.⁵⁷

Preservation solutions can be categorized as intracellular or extracellular solutions based on their overall sodium and potassium concentrations. Intracellular solutions have high concentrations of potassium and low concentrations of sodium in order to mimic the cellular milieu and minimize concentration gradients across cellular membranes that could favor the efflux of potassium from the donor organ cells. These solutions include the Euro Collins solution and the University of Wisconsin solution. However, concerns have been raised that high-potassium concentrations may lead to vasoconstriction within the donor organ, particularly in the pulmonary vasculature. These concerns led to the development of extracellular (low-potassium concentration) solutions such as histidine-tryptophan-ketoglutarate and Celsior flushing and cold storage solution (Sanofi, Bridgewater, NJ). To date, no consensus has been reached regarding the equivalence of intracellular and extracellular preservation solutions.⁵⁷

Although a full review of preservation solutions is outside the scope of this article, recent articles have reviewed these solutions in-depth.⁵⁷⁻⁵⁹

Discussion

The care given to one organ donor is tantamount to the care of several transplant recipients. Aggressive donor management ensures that the largest number of organs can be successfully procured and improves the organs' overall quality. Together, the interventions outlined in this article contribute to the stability of the donor, as well as the eventual outcomes for organ transplant recipients. By fostering a greater understanding of these medications and the literature surrounding their use, pharmacists in a wide variety of hospital settings will be better prepared to provide for these donors and ultimately contribute to the donor's ability to provide their final gift.

Conclusion

It is essential to provide optimal

pharmacotherapy for each potential organ donor to ensure organ recovery and donation. Typical medications used in organ donors include agents for blood pressure management and fluid resuscitation, medications necessary for electrolyte management, blood products, vasopressors, hormone replacement therapy, anti-infectives, anticoagulants, paralytics, and organ preservation solutions.

Disclosures

The authors have declared no potential conflicts of interest.

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