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CAMPRAL®: A NEW APPROACH FOR THE TREATMENT OF ALCOHOL DEPENDENCY

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Alcohol abuse has a dramatic impact on many lives. Annually, more than 100,000 deaths are alcohol-related.¹ Approximately 7.4% of Americans meet the diagnostic criteria for alcohol abuse or alcoholism. The economic burden of alcohol abuse to society exceeds that of both illicit drug or tobacco abuse.¹ The annual cost associated with alcohol abuse was estimated at \$184.6 billion in 1998.¹ The disease's major economic impact is on productivity losses due to alcohol-related illness and premature death. Over \$26 billion of the total cost of alcohol abuse is related to treatment and prevention. Medical care costs for this sector are up to three times more than that of the general population. Fifty percent of all alcohol is consumed by 10% of the drinking population. The burden of disease is age-related. More people drink heavily in the 21- to 34-year age group while those over 65 years old drink the least. The mental and physical behaviors induced by alcohol involve the serotonergic, noradrenergic, and GABAergic receptor systems. The GABAergic system appears to be responsible for the action of alcohol on the central nervous system.

Cirrhosis of the liver and hepatic impairment are the most common complications of alco-

holism. Alcoholic hepatitis and alcoholic cirrhosis develop in approximately 15-20 percent of chronic alcoholics. Liver disease can progress to fulminant hepatic failure and gastrointestinal hemorrhage, infection, or kidney failure. Also, liver transplantation is prohibited for patients who abuse alcohol.

The FDA approved acamprosate (Campral®) on July 29th, 2004. It is indicated for the maintenance of abstinence from alcohol in alcoholics who are abstinent at treatment initiation. Acamprosate has been a therapeutic option in other countries for some time and is currently available in more than 20 countries. The four manufacturers who are currently distributing acamprosate are Forest, Merck, Lipha, and Almirall. The four available brand names for acamprosate are Campral® (Forest), Sobrial® (Merck), Aotal® (Lipha), and Almirall® (Almirall). Acamprosate is marketed as Campral® by Forest Pharmaceuticals in the United States.

The objectives of this article are to discuss the pharmacology, pharmacokinetics, and clinical trials involving acamprosate as well as to review information pertinent to the effective integration of this agent into clinical practice.

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Pharmacology and Pharmacokinetics

The mechanism of action of acamprosate is not completely understood. GABA-mimetic drugs such as acamprosate reduce alcohol withdrawal symptoms whereas antagonists produce symptoms similar to those observed during alcohol withdrawal. The mechanism of action for acamprosate is believed to involve stimulation of GABAergic neurotransmission in the brain. It may also antagonize the effects of certain excitatory amino acids. It is active at postsynaptic GABA(B) receptors that decrease electrical excitability, though it does not change membrane potential.

The bioavailability of acamprosate is approximately 11%.³ The rate of absorption is slow and food reduces its absorption. However, this effect does not appear to be clinically significant, and no dosage adjustments are needed. Acamprosate crosses the blood-brain barrier; therefore, it is expected that adverse reactions will involve the central nervous system. There are no active metabolites and the major route of excretion is renal.

Clinical Trials

A double-blind, placebo-controlled, 24-week study evaluated the efficacy and safety of acamprosate in the treatment of alcohol dependence.⁴ The sample comprised 75 patients, 18-60 years of age, diagnosed with alcohol dependence. The patients were randomly divided into two groups one week after alcohol cessation and treated with either acamprosate 1998 mg/day in 3 divided doses or placebo. During the first 12 weeks, patients did not receive any additional medications. The main outcome measures were relapse rates, side effects and time to first relapse. Statistically, the effect of acamprosate on preventing relapse rates was significantly greater than placebo ($p = .02$). The investigators concluded that acamprosate is an effective treatment for alcohol dependence.

A 6-month, randomized controlled study compared acamprosate with placebo in preventing relapse after withdrawal from alcohol. The study was done in 20 locations throughout England.⁵ Patients with alcohol-dependence were detoxified within the first 5 weeks and randomly assigned to treatment with either acamprosate 666 mg three times daily or matching placebo. A total of 581

individuals qualified for the study. One-third of the patients were episodic drinkers, 84% were male, and 44% were unmarried. On average, medication was begun 24 days after the start of detoxification. Thirty-two percent of patients had relapsed and recommenced drinking at this point. The 6-month study period was completed by 35% of patients. Adverse events led to withdrawal in 14% of acamprosate-treated patients and 9% of placebo-treated patients. Compliance was poor during the study. Only 57% of patients were taking at least 90% of their tablets by week 2. The mean total number of abstinent days was 77 in the treatment group and 81 in the control group ($p > 0.05$). Complete abstinence for 6 months was achieved by 12% in the acamprosate group and 11% of the placebo group ($p > 0.05$). However, the mean percentage reduction in alcohol craving measured via visual analogue scale was greater in the acamprosate group at week 2 and week 4 ($p < 0.001$), and the mean decrease in the Hamilton Anxiety score at week 4 was greater in the acamprosate than placebo patients ($p = 0.017$). Compared with other published trials of acamprosate, treatment was initiated later in the cessation process, more patients had relapsed before medication was started, and the drop-out rate was higher. This may have contributed to the lack of a more impressive treatment effect in the study.⁹

A one-year study was designed to evaluate the effectiveness of acamprosate as a treatment to maintain abstinence in alcohol-dependent patients. Within three weeks after cessation, 272 patients entered a randomized, double-blind, placebo-controlled study.⁶ Patients received either acamprosate or placebo for 48 weeks. Following the 48-week treatment-phase, patients were followed without medication for an additional 48 weeks. Patients who were receiving acamprosate showed a significantly higher abstinence rate within the first 60 days of treatment compared with patients who were assigned to placebo (67% vs. 50%, $P < 0.05$). The effect was maintained through completion of the treatment period (43% vs. 21%, $p = .005$). Subjects treated with acamprosate also had significantly longer mean abstinence duration, 224 vs. 163 days (62% vs. 45% days abstinent, $p < .001$). However, there was no difference in psychiatric symptoms. Of the patients who received acamprosate, 41% dropped out, compared to 60% of placebo-treated

Table 1. Percent of Alcohol Dependent Subjects with Adverse Events by Medication Treatment Assignment

Body System	Placebo	Acamprosate 1332 mg/d	Acamprosate 1998 mg/d	Acamprosate Pooled
Number of subjects	1706	397	1539	2039
Number with adverse event (%)	955 (56)	248 (62)	910 (59)	1231 (61)
Body as a Whole	517 (30)	121 (30)	513 (33)	685 (34)
Digestive System				
Nausea	58 (3)	11 (3)	69 (4)	87 (4)
Diarrhea	166 (10)	39 (10)	257 (17)	329 (16)
Anorexia	44 (3)	20 (5)	35 (2)	57 (3)
Nervous System				
Anxiety	98 (6)	32 (8)	80 (5)	118 (6)
Dizziness	44 (3)	15 (4)	49 (3)	67 (3)
Insomnia	121 (7)	34 (9)	94 (6)	137 (7)
Skin and Appendages	169 (10)	34 (9)	994 (6)	137 (7)

patients. At the end of the 48-week observation phase, 39% and 17% of the acamprosate- and placebo-treated patients, respectively, had remained abstinent ($p = .003$). Acamprosate appeared to be a safe and effective adjunct in treating alcohol-dependent patients and in maintaining abstinence at 2 years.

Naltrexone and acamprosate are thought to provide benefits in relapse prevention of alcoholism through unique mechanisms. A controlled study was conducted to explore whether differences exist in the efficacy of the two drugs and whether the combination offers any advantage. After the cessation of alcohol abuse, 160 patients with alcoholism participated in a randomized, double-blind, placebo-controlled protocol. Patients were divided into four groups: naltrexone, acamprosate, naltrexone and acamprosate, or placebo.⁷ Patients were assessed weekly for 12 weeks by interview, self-report, questionnaires, and laboratory screening. The primary outcomes were time to first drink, time to relapse, and the cumulative abstinence time. Time-to-event analyses were used to examine the non-relapse rates for the 4 treatment groups for lapse events, such as time to first drink. They revealed statistically significant differences among the treatment groups ($p < 0.001$). Significant differences emerged between naltrexone and placebo ($p = 0.03$), between acamprosate and placebo ($p =$

0.04), and between dual therapy and placebo ($p = 0.002$). There was no significant difference in time to first drink between naltrexone and acamprosate. The combined medication was significantly more effective than acamprosate alone ($p = 0.04$) but not different from naltrexone alone. In summary, the combination was more effective than placebo and acamprosate but similar to naltrexone, thus the merit of combination treatment requires further study.

Dosing and Administration

Treatment with acamprosate should be part of a comprehensive treatment program that includes psychosocial support. The approved dose of acamprosate is 666 mg three times daily. A lower dose may be effective in some patients. Alternative dosage regimens have been used in some studies.⁴ One study used 1332 mg/day in patients lighter than 60 kg, administered as 666 mg in the morning, 333 mg in the afternoon, and 333 mg in the evening. Acamprosate is not approved for use in children or adolescents. Acamprosate may be dosed without regard to meals; however, dosing with meals was used in clinical trials, and it may help with compliance in patients who regularly eat three meals daily.

Acamprosate is contraindicated in patients with severe renal insufficiency, defined as a

creatinine clearance less than 30 mL/min. Patients with a creatinine clearance between 30 and 50 mL/min should receive 333 mg three times daily, half the usual maintenance dose. Since acamprosate is not metabolized by the liver, dosage alterations are not necessary in patients with mild to moderate hepatic impairment.

Adverse Drug Reaction (ADR)

Adverse reactions are common in acamprosate-treated patients. Some of the most common are nausea, diarrhea, headache, and fatigue. The Combining Medications and Behavioral Interventions (COMBINE) study allows for comparison of ADRs across patients treated with acamprosate, naltrexone, and placebo.⁸ Seventeen different types of ADRs were systematically recorded. Physical complaints and symptoms are significant within this population (Table 1). One subject in the naltrexone group and one subject in the acamprosate group could not tolerate the medication because of adverse effects.

In another study, 288 patients were randomized to acamprosate or placebo.¹² The overall incidence of adverse events was similar in both groups. However, there was a trend for gastrointestinal symptoms to be reported more frequently in the acamprosate-treated group (n = 61) versus placebo-treated patients (n = 46). Other symptoms that were reported more frequently in the acamprosate-treated patients included diarrhea, dyspepsia, constipation, and flatulence.

A trial performed in 18 different outpatient centers in Italy enrolled 330 subjects.¹³ One group was treated with standard dose acamprosate and the other group was treated with placebo. The most common ADR was headache (7.3% in acamprosate group and 6.6% in placebo group), diarrhea (3.0% in acamprosate patients and 2.4% in placebo patients), and gastrointestinal discomfort (1.2% of acamprosate patients and 5.6% in placebo group). There was no significant difference between the two treatment groups. In both COMBINE and the Italian study gastrointestinal complaints occurred numerically less frequently; however, this pattern was not supported in the study by Gual et al.¹²

Cost

The average retail cost for a one month sup-

ply of acamprosate, based on a survey of three retail pharmacies in Gainesville, FL, is \$134.64.

Summary

The likelihood of maintaining abstinence from alcohol is increased if acamprosate is administered as an adjunct to a comprehensive abstinence program. Clinical trials have shown that patients treated with acamprosate experience lower relapse rates compared with those who do not receive pharmacological intervention. The combination of acamprosate and naltrexone may offer additional benefit over acamprosate alone, but did not appear more effective than naltrexone. Thus, additional studies are needed to fully elucidate the role of combination drug therapy in this population. In conclusion, acamprosate is a welcomed addition to the limited repertoire of drugs to treat alcohol dependence. Because it is renally eliminated and does not appear to cause hepatic injury, acamprosate offers patients with hepatic impairment an alternative to naltrexone. Health professionals should consider acamprosate as an adjunct to cognitive behavioral therapy for increasing the likelihood of long-term abstinence from alcohol.

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OVERVIEW OF VASOPRESSORS AND INOTROPES IN THE ICU

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Intensive care units (ICU) are faced with an ever growing influx of patients. Moreover, patients admitted to the ICU are much sicker than in past years, making the safe and effective use of vasopressors and inotropes of paramount importance. Given the ambiguity and relative obscurity of these agents paired with the degree of complexity of severely ill patients, it is no surprise that selecting the optimal agent can be a daunting task. Unfortunately, there are no guidelines to facilitate this process. The intent of this article is to streamline information on vasopressors and positive inotropes into a comprehensive model.

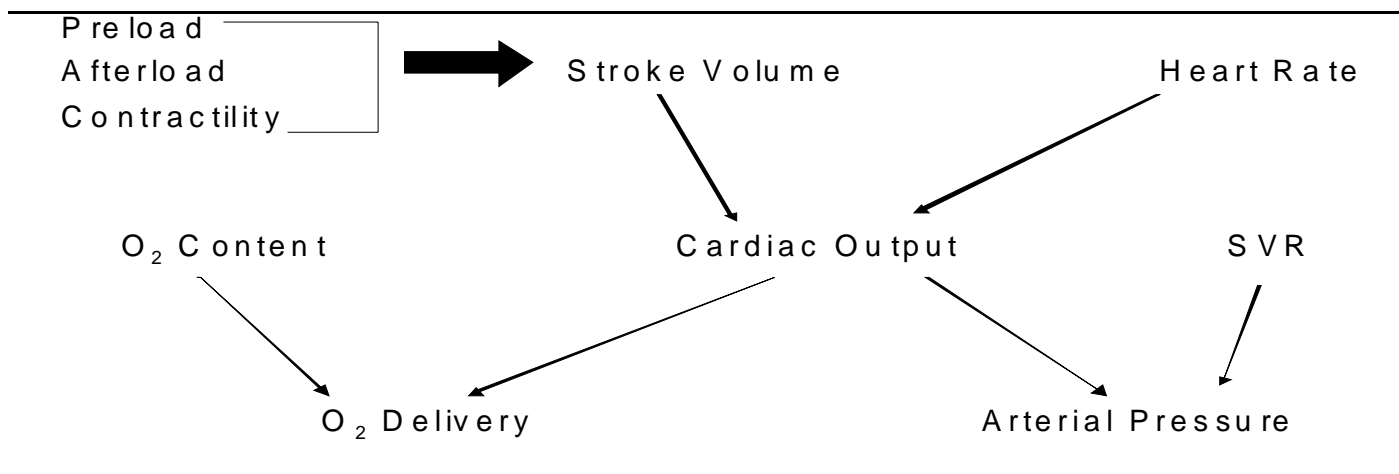
Indications for use

In the acute setting, many situations arise in which vasopressors and inotropes are life saving. These situations include, but are not limited to, shock, advanced cardiac life support (ACLS), and bradycardia. There are a multitude of patient-specific factors that should be considered when deciding which agent to prescribe. These considerations include heart rate (HR), blood pressure (BP), pulse, cardiac output (CO), cardiac index (CI), right arterial pressure (RAP), pulmonary capillary wedge pressure (PCWP), and pH. A working knowledge of these parameters and knowing how individual pharmacological agents influence them will facilitate appropriate drug selection (Figure 1).

Norepinephrine

Norepinephrine acts as a potent α_1 -adrenergic agonist, though it activates β_1 -adrenergic receptors to a lesser degree (Table 1 and Figure 2). Arteriolar vasoconstriction is mediated by α_1 -receptor activation, thereby increasing sys-

Figure 1. Primary Determinants of Cardiac Output, Arterial Pressure, and Oxygen Delivery



temic vascular resistance (SVR)¹ (Table 2). This increase in SVR results in an increase in systemic arterial and coronary perfusion pressures. Secondly, activation of β_1 receptors in the myocardium increases contractility and stroke volume. Heart rate and CO usually do not change; in fact, a slight decrease in CO may accompany the increase in afterload and perfusion pressure. As a result of increased BP, particularly diastolic, myocardial oxygen consumption is increased. Consequently, myocardial ischemia and arrhythmias may be intensified or provoked, and left ventricular function compromised.² Norepinephrine is commonly used in the treatment of acute hypotension resulting from conditions such as myocardial infarction, septicemia, and spinal anesthesia.²

Phenylephrine

Phenylephrine functions as a pure α_1 agonist, increasing both systolic and diastolic BP. As a result of increased BP, afterload and myocardial oxygen consumption are increased (Table 1 and Figure 2).² Phenylephrine may be especially useful in refractory hypotension complicated by atrial or ventricular arrhythmias because it has minimal direct effects on the heart.³ On the other hand, this medication must be used cautiously in patients with decreased CO due to the loss of capillary hydrostatic pressure, resulting in decreased preload. This action, along with reflex bradycardia and increased afterload, may further reduce CO in an already compromised patient.²

Dopamine

Dopamine is often considered a first line

agent in multiple conditions due to its various inotropic, chronotropic, and vasoactive properties. A mixture of activity is seen in a dose-dependent manner (Table 1 and Figure 2). At low doses, the primary effect of dopamine is on β_1 receptors. This leads to increased ventricular contractility and HR. Tachycardia and tachydysrhythmias can occur in patients treated with dopamine, especially in the elderly, those with preexisting or concurrent cardiac ischemia or dysrhythmias, and when administered concomitantly with other arrhythmogenic agents. As the dose is increased, activity shifts to include α_1 receptors, eliciting an increase in arterial pressure and SVR. Dopamine is generally preferred in patients with depressed CO, normal to moderately elevated PCWP, and moderate to severe hypotension.²

Epinephrine

Epinephrine is a mixed α_1/β_1 agonist. It acts as a vasoconstrictor, and a positive inotropic and chronotropic agent (Table 1 and Figure 2). At low doses, β_1 -adrenoceptor effects are most prevalent, leading to increased HR and contractility. This leads to an increase in CO that further increases systolic BP (Figure 1). If higher doses are administered, α_1 agonist activity predominates and vasoconstrictive effects become more apparent.⁴

Dobutamine

Dobutamine is a positive inotrope that works primarily through β_1 -receptors and, to a lesser extent, through α_1 - and β_2 -receptors (Table 1 and Figure 2).² These actions increase stroke index,

Table 1. Receptor Profile and Clinical Response of Select Medications Applied in the Setting of Shock.

Drug	Usual Dose	Receptor Specificity			Pharmacologic Response			
		α_1	β_1	β_2	VD	VC	INT	CHT
Milrinone	0.75 mg/kg bolus, then 5-20 ug/kg/min	0	0	0	+	0	+++	+
Dobutamine	2.5-15 μ g/kg/min	+	+++	++	++	0	+++	+
Dopamine	0.5-2 μ g/kg/min	0	0	0	0	0	0	0
	2-5 μ g/kg/min	0	+	0	0	+	+	+
	5-10 μ g/kg/min	+	++	0	0	++	++	++
	15-20 μ g/kg/min	+++	+++	0	0	+++	++	++
Epinephrine	0.01-0.1 μ g/kg/min	+	+++	++	++	0	+++	++
	0.1 μ g/kg/min	+++	++	++	0	+++	++	++
Isoproterenol	0.01-0.1 μ g/kg/min	0-	++++	+++	+++	0	+++	+++
Norepinephrine	2-10 μ g/min (0.5-1 μ g/kg/min)	++++	++	0-	0	++++	+	+
	Titrate to SBP 90-100mm Hg							
Phenylephrine	20-200 μ g/min Titrate to effect	+++	0-	0	0	+++	0	0

VD = Peripheral vascular vasodilatation; VC = Peripheral vascular vasoconstriction; INT = Positive inotropy; CHT = Positive chronotropy
Scale: (0) no effect, (+) weak, (++) mild, (+++) moderate, (++++) strong. Adapted from Reference 2

left ventricular stroke work index, CI and oxygen delivery without increasing the pulmonary artery occlusion pressure. Dopamine and dobutamine are often considered in similar settings, heart failure for example. One noteworthy difference is that while dopamine increases pulmonary artery occlusion pressure, dobutamine does not. Dobutamine's most prominent effects occur in patients with low CO and high filling pressures,³ making dobutamine an acceptable option in the setting of low output states. Using dobutamine as a single agent to increase BP may be of limited value due to compensatory vasodilatation and β_2 -receptor activation.⁵ In this situation, a combination of dobutamine along with another catecholamine with more predominant α adrenergic receptor-mediated effects may be used. In patients with decompensated heart failure who are concomitantly treated with β -blockers it is possible that response to dobutamine will be poor since these two agents exert antagonistic effects.

Milrinone

Milrinone is referred to as an "inodilator"

because it has both positive inotropic ("ino-") and vasodilatory ("dilator) effects (Table 1 and Figure 2). The distinction between this agent and many others is that milrinone does not work through α or β receptors. This drug inhibits the enzyme phosphodiesterase, thereby increasing cAMP leading to inotropic and vasodilatory properties, which increase stroke volume and CO. There is often little change in HR. Despite the increase in CI, mean arterial pressure decreases due to peripheral vasodilation.⁶ This action could possibly lead to reflex tachycardia. Milrinone should be used in patients with a low CI, adequate BP, and an elevated left ventricular filling pressure.³ Milrinone is the preferred inotrope in patients with decompensated heart failure receiving β -blockers.

Isoproterenol

Isoproterenol is a mixed β_1/β_2 -adrenergic receptor agonist that may be used in situations of atrioventricular block or bradycardia (Table 1 and Figure 2).⁷ This medication has fallen out of favor of late because of the potential it has to cause tach-

Figure 2. The Sympathomimetic Spectrum.



yarrythmias. Further, the availability of other agents such as atropine and nonpharmacological modalities such as pacing are more effective and safer to use.

Vasopressin

Vasopressin is unique in that it does not work on the same receptor system as any of the aforementioned medications. Mechanistically, vasopressin works on V-1 receptors on the arterial smooth muscle and V-2 receptors found in renal tubules. Vasopressin effectively increases arterial BP and SVR through vasoconstriction. It is often applied as a last line agent in patients who have received adequate fluid resuscitation and are refractory to other vasopressors. In this circumstance, it is usually added to existing therapies.⁸ This medication may also be used as an alternative to epinephrine for the treatment of cardiac arrest during ACLS.⁹ Vasopressin should be avoided in patients with hypovolemia, cardiogenic shock or septic shock with myocardial depression. In this setting, it may further decrease CO and cause profound cutaneous vasoconstriction and necrosis.¹⁰

Selection of a Vasopressor or Inotrope

The following case vignettes are intended to provide examples of how these agents might be selected in certain situations. The discussion focuses on pharmacological interventions and does not represent all of the actions that should be initiated in such patients. In most cases, there are several appropriate actions.

Cardiogenic Shock

AL is a 58 year-old Caucasian female who recently underwent four-vessel coronary artery bypass graft (CABG) surgery and is now in the ICU. Her vital signs are stable with a mean arterial pressure of 63 mm Hg. AL's past medical history includes two myocardial infarctions and hypertension. Current medications include nitroglycerin, metoprolol, hydrochlorothiazide, aspirin, and simvastatin. Forty-five minutes after admission to the ICU AL's BP dropped. Her hemodynamic profile was as follows: BP 90/50 mm Hg; pulse 108 beats/min; CO 2.8 L/min; CI 1.65 L/min/m²; PCWP 22 mm Hg; RAP 12 mm Hg; pH 7.38; HCO₃ 20 mEq/L; respiratory rate 26/min; urine output 25mL/hr; temp 36°C (normal values seen in Table 3).

Assessment of AL's clinical presentation suggests that she was experiencing decompensated heart failure which resulted in cardiogenic shock. The hemodynamic criteria consistent with cardiogenic shock are hypotension with a systolic BP <90 mm Hg, a reduced cardiac index of <2.2 L/min/m², and the presence of elevated PCWP of >15 mm Hg.¹¹ According to AL's presentation, dopamine could be initiated at a dose of 3 μ g/kg/min based on its ability to directly stimulate β_1 adrenergic receptors. This effect will increase stroke volume, HR and CO. The goal of therapy is to increase CI to at least 2.5 L/min/m² and to maintain MAP around 80 mm Hg depending on clinical signs of hypoperfusion, reduce PCWP, while maintaining HR below than 125 beats per minute. Due to dopamine's rapid onset of action, it may be titrated upward at a rate

Table 2. Adrenoreceptor Types and Location.

Receptor Type	Location	Response when stimulated
α_1	Arteries, arterioles, veins	Constriction
α_2	Gastrointestinal tract	Decreased tone, motility, and secretions
β_1	Heart	Increased heart rate and force of contraction
β_2	Skeletal muscle vasculature	Dilation
	Coronary arteries	Dilation
	Bronchial smooth muscle	Dilation

Adapted from reference 4.

of 1-2 $\mu\text{g}/\text{kg}/\text{min}$ every 10 minutes depending on the hemodynamic data and clinical status. A rate of greater than 10 $\mu\text{g}/\text{kg}/\text{min}$ might be considered a threshold in this case, given dopamine's tendency to increase left ventricular filling pressure, which may exacerbate pulmonary edema. Patients should be monitored for tachycardia, anginal pain, arrhythmias, headache, hypertension, vasoconstriction, nausea and vomiting.²

Septic Shock

PD is a 57 year-old Asian male admitted to the ICU five days ago with a chief complaint of acute abdominal pain for three days, bloody diarrhea, fever, tachypnea, and hypotension. A diagnosis of superior mesenteric artery occlusion with necrotic bowel was established. Following diagnosis, PD underwent surgery for removal of necrotic bowel tissue. Between days 1 and 4 of postoperatively, there was a continual climb in serum creatinine and the patient could not be completely weaned from ventilatory support. His vital signs were stable and appropriate antibiotic treatment was implemented. PD has a past medical history that is positive for CHF and coronary artery disease with stable angina pectoris that had been treated with carvedilol, enalapril, digoxin, furosemide, and NTG tablets. On postoperative day 5, PD complained of chills and was noted to have a fever of 39.4°C. Physical findings included: BP 98/60 mm

Table 3. Normal Hemodynamic Values and Indices.

Blood Pressure	120-140/80-90 mm Hg
Cardiac Output	4-7 L/min
Heart Rate	60-80 beats/min (BPM)
Pulmonary Capillary Wedge Pressure (PCWP)	5-12 mm Hg
Cardiac index	2.5-4.2 L/min/m ²
Mean Arterial Pressure (MAP)	80-100 mm Hg
Stroke Volume (SV)	60-130 mL/beat
Right Arterial pressure	2-6 mm Hg
Pulmonary Vascular Resistance (PVR)	20-120 dynes*sec*cm ⁻⁵
Systemic Vascular resistance (SVR)	800-1440 dynes*sec*cm ⁻⁵

Hg; pulse 126 beats/min; RR 27 beats/min; urine output decreased to 25 mL/hr and absent bowel sounds. A chest X-ray was performed that showed an enlarged heart with bilateral pulmonary infiltrates and right lower lobe atelectasis. Over a short time period, PD became confused and disoriented. Urine, sputum, and blood samples were sent for culture and sensitivity. A 500 mL normal saline fluid bolus was given and pulmonary and arterial catheters were inserted. The following hemodynamic profile was obtained: BP 90/50 mm Hg; pulse 118 beats/min; CO 6.2 L/min; CI 3.5 L/min/m²; RAP 8 mm Hg; PCWP 11 mm Hg; SVR 733 dyne*sec*cm⁻⁵; inspiratory oxygen concentration of 40%; PaO₂ 76 mm Hg; PaCO₂ 34 mm Hg; pH 7.3.

PD expressed signs and symptoms consistent with septic shock that included hypotension, tachycardia, low SVR, worsening heart function, declining urinary output, altered sensory perception, spiking fever, and his CO was on the upper end of normal. Even though CO of 6.2 L/min is on the upper end of normal for a patient in septic shock, it is not sufficient in this case to perfuse essential organs, evidenced by the SVR of 733 dyne*sec*cm⁻⁵. In addition, PD had metabolic acidosis, which indicated the presence of anaerobic metabolism, and a CO that is insufficient to meet the oxygen demand.

When treating septic shock there are three primary considerations. First is eradication of the source of infection; second, hemodynamic support; and thirdly, inhibition or attenuation of the initia-

tors and mediators of sepsis.²

After appropriate antibiotic treatment and fluid boluses were given to PD, focus should be shifted to other areas of hemodynamic support. Dopamine is the initial vasopressor of choice, but dobutamine has also been utilized based on its similarity to dopamine (increased CO and mean arterial pressure). The advantage of dobutamine is its ability to lower PCWP, decrease myocardial oxygen consumption, and cause less pulmonary shunting than dopamine; however, dopamine's α_1 receptor activity may provide much needed additional vasopressor support. Dobutamine could be considered initially at a rate of 2.5 $\mu\text{g}/\text{kg}/\text{min}$ in PD because his CO was below 3.5 L/min/m². This dose may be titrated upwards every five to ten minutes, according to PD's response, to 15 or 20 $\mu\text{g}/\text{kg}/\text{min}$.

When a patient presents to the ICU, there are many factors that must be addressed. Most patients will not fall neatly into the shock classes; instead, the various reasons for instability must be considered when selecting an initial agent. If the patient has not stabilized within a short period of time, another agent may be added. Combination therapy will often be necessary to take advantage of different receptor systems in the pursuit of hemodynamic equilibrium.

Summary

There are various vasopressors and inotropes used to treat shock. Confusion arises due to the numerous mechanisms of action that these agents work through and the diverse ways that the human body responds to them. The most important aspect in the process of choosing an appropriate agent is to consider individual patient factors and clinical presentations. Each agent should be chosen based on its ability to directly or indirectly affect the most vital area of concern while having minimal impact on unrelated organ systems. In many cases, one agent is insufficient to resolve all hemodynamic derangements and additional agents must be added. In such instances, agents that work via an alternate receptor system should be selected. Integration of these considerations and concepts will hopefully facilitate selection of an optimal pharmacological regimen.

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