Medicines Used in the Emergency Department and Dosage Guide

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Preface

Emergency departments represent one of the most dynamic settings in modern medicine, where the most critical decisions are made. In this environment, clinical success depends not only on theoretical knowledge but also on the ability to make rapid, accurate, and evidence-based pharmacological decisions. In this context, drug selection, dose adjustment, and administration strategies are among the fundamental factors that directly influence patient outcomes.

This work, titled Medicines Used in the Emergency Department and Dosage Guide, has been prepared with the aim of presenting, in a systematic and comprehensive manner, the pharmacological properties, clinical indications, and particularly the dosing approaches specific to emergency department practice for medications frequently used in emergency medicine. The book not only conveys theoretical knowledge but also aspires to serve as a practical and applicable guide that supports clinical decision-making processes.

One of the most distinctive features of this work is the adoption of a structured and standardized section format for each medication. The sections are systematically organized under headings such as introduction, pharmacodynamic and pharmacokinetic properties, general and emergency department–specific indications, detailed dosing protocols, use in special patient populations, adverse effects, toxicity management, and clinical pearls. In particular, emergency department indications and disease-specific dosing strategies are presented in detail in accordance with current guidelines and evidence-based approaches.

Considering that time is limited and decisions are critical in emergency medicine practice, the aim of this book is to provide physicians, residents, and healthcare professionals with a fast-access, reliable, and practical reference source. At the same time, this work seeks to contribute to the academic literature and to become a reference resource at the international level through the presentation of standardized information.

We would like to thank all the chapter authors who contributed to the preparation of this book for their scientific input and meticulous work. Each chapter has been prepared by experienced academics in their respective fields, in light of current literature and clinical experience.

Cemil KAVALCI, Prof., MD, and the Editorial Board
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Chapter 6

Anticoagulant and Antithrombotic Medicines

Ahmet Şenol

ABSTRACT

Anticoagulant and antithrombotic therapies play a central role in contemporary cardiovascular, neurological, and emergency care.[1] These medications are essential for the prevention and treatment of thromboembolic diseases such as venous thromboembolism, stroke associated with atrial fibrillation, acute coronary syndromes, and prosthetic valve thrombosis.[2] This chapter presents an evidence-based overview of clinically relevant anticoagulant and antiplatelet therapies. including unfractionated heparin, low-molecular-weight heparins (enoxaparin, tinzaparin), vitamin K antagonists (warfarin), direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban), and antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor).[3] Each agent is discussed individually with respect to pharmacology, clinical indications, dosing strategies, safety profiles, contraindications, toxicity management, and practical clinical considerations. Particular attention is given to high-risk groups such as older adults, patients with renal or hepatic impairment, and pregnant individuals.[4] In addition, recent developments in personalized medicine and risk stratification tools have further refined the selection and monitoring of antithrombotic therapies, improving patient-specific outcomes while minimizing complications.

INTRODUCTION

Thrombotic diseases remain a significant cause of morbidity and mortality worldwide and continue to challenge healthcare systems.[1] Pathologic thrombus formation results from complex interactions between platelet activity, the coagulation cascade, and endothelial function.[2] Targeting these mechanisms therapeutically has significantly reduced the occurrence of major cardiovascular and thromboembolic complications, including ischemic stroke, myocardial infarction, pulmonary embolism, and systemic embolization.[3] Furthermore, demographic shifts such as population aging and the increasing prevalence of chronic comorbid conditions have amplified the need for effective and sustainable long-term antithrombotic management strategies in modern clinical practice.

Anticoagulants primarily inhibit the coagulation cascade, whereas antiplatelet agents target platelet activation and aggregation.[4] Appropriate use of these agents requires a detailed understanding of their mechanisms of action, pharmacokinetics, safety profiles, and patient-specific risk factors.[5] In acute care settings, rapid onset and reversibility are critical, whereas long-term therapy emphasizes safety, adherence, and prevention of bleeding complications. Therefore, clinicians must balance thrombotic risk against bleeding risk using validated clinical scoring systems and individualized treatment approaches.[6]

PHARMACOLOGY OVERVIEW

Anticoagulants

Anticoagulants act by inhibiting key stages of the coagulation cascade involved in thrombus development, thereby preventing thrombus formation and propagation.[5] Unfractionated heparin and low-molecular-weight heparins primarily enhance the activity of antithrombin, resulting in inhibition of thrombin and factor Xa.[7] In contrast, warfarin reduces the hepatic synthesis of vitamin K-dependent clotting factors, leading to a delayed but sustained anticoagulant effect.[8] Direct oral anticoagulants (DOACs) work through selective inhibition of thrombin or factor Xa , and are characterized by more predictable pharmacokinetic and pharmacodynamic profiles, thereby limiting the requirement for routine laboratory monitoring in many patients.[9] Additionally, variability in patient response and potential drug-drug interactions must be carefully considered, especially in individuals receiving complex therapeutic regimens.

Antiplatelet Agents

Antiplatelet drugs reduce arterial thrombosis primarily by suppressing platelet activation and aggregation pathways.[10] The antiplatelet activity of aspirin results from irreversible inhibition of cyclooxygenase-1 and subsequent suppression of thromboxane A_2 synthesis.[11] $P2Y_{12}$ receptor inhibitors block ADP-mediated platelet aggregation and play a central role in acute coronary syndrome management. In addition, emerging antiplatelet strategies focus on optimizing dual and triple therapy durations to reduce bleeding complications without compromising efficacy.[12]

CLINICAL INDICATIONS

Antithrombotic therapy is widely used for the treatment and prevention of venous thromboembolism, stroke prevention in atrial fibrillation, acute coronary syndromes, mechanical valve thrombosis, perioperative prophylaxis, and certain hypercoagulable conditions.[2,5] Choice of agent depends on clinical context, comorbidities, bleeding risk, renal and hepatic function, and patient preference. Clinical decision-making should also incorporate dynamic risk assessment models that evolve throughout the course of the disease and treatment period.[6]

DOSING AND ADMINISTRATION

Accurate dosing is essential to achieve therapeutic efficacy while minimizing adverse events, particularly in critically ill patients where pharmacokinetics may be altered.

Unfractionated Heparin (UFH)

Indications include acute coronary syndromes, venous thromboembolism, and peri-procedural anticoagulation.[7] Initial therapy typically involves a 60-80 U/kg intravenous bolus, after which a continuous infusion of 12-18 U/kg/h is administered and titrated

Chapter 7

Oxygen Therapy and Noninvasive Application Methods

Kadir Yenal

ABSTRACT

Oxygen therapy plays a crucial role in managing critically ill patients by correcting low blood oxygen levels and supporting cellular oxygenation. On the other hand, improper, needless, or excessive oxygen usage can result in serious problems such oxidative stress, hypercapnia, absorption atelectasis, and elevated mortality. Consequently, oxygen should not be seen as a "harmless gas," but rather as a pharmacological substance that must be supplied based on the indication, dosage, and target saturation levels. In modern clinical practice, ventilation-perfusion matching, hemoglobin level, cardiac output, and FiO_2 correction form the physiological basis of oxygen therapy. According to current guidelines, most patients should maintain SpO_2 values between 92 and 96%, while those with conditions like COPD that increase the risk of hypercapnia should aim for a range of 88 to 92%. The potential of non-invasive oxygen delivery techniques, such as nasal cannula, simple face mask, Venturi mask, high-flow nasal oxygen (HFNO), and non-invasive ventilation (NIV), to decrease the need for intubation, enhance patient comfort, and shorten stays in the intensive care unit (ICU) for acute respiratory failure is making them more popular. However, in cases of sepsis, acute coronary syndrome, cardiogenic pulmonary edema, and the peri-intubation interval, liberal oxygen techniques do not improve clinical outcomes and may significantly raise the risk of neurological and vascular sequelae. The physiological principles of oxygen treatment, its therapeutic indications, dosage and administration guidelines, safety profile, toxicity mechanisms, and other evidence-based respiratory support techniques are all covered in this section. Results show that to prevent the negative effects of hypoxemia and hyperoxia, oxygen therapy must be given using a targeted, titration-based, and customized approach based on patient characteristics.

INTRODUCTION

Oxygen therapy is one of the most fundamental interventions in acute and critical care medicine. Its primary purpose is to correct tissue hypoxia by increasing the partial pressure of oxygen in arterial blood, thereby supporting cellular metabolism and organ function. Inadequate or excessive oxygen supply can result in major consequences such oxidative stress, hypercapnia in certain patients, absorption atelectasis, and increased mortality in specific patient groups, even though oxygen is typically regarded as a harmless and universally useful medication. Thus, it is essential in contemporary emergency room practice to comprehend oxygen delivery systems, dose modification techniques, and evidence-based threshold values. On-invasive oxygen delivery methods-nasal cannula, simple face mask, Venturi mask, high-flow nasal oxygen (HFNO), and non-invasive ventilation (NIV)-have reduced intubation rates, shortened intensive care unit stays, and improved patient-centered outcomes in the management of acute respiratory failure.[1]

Respiratory system diseases represent a significant global public health burden in terms of morbidity and mortality; in 2019, approximately 2.4 million deaths were attributed to lower respiratory tract infections, with a total of 488.9 million incidence cases reported. This reality underscores the critical importance of adequate oxygen therapy and appropriate non-invasive oxygen delivery strategies on a global scale.[2]

PHYSIOLOGICAL BASIS OF OXYGEN THERAPY

Oxygen is essential for oxidative phosphorylation in the mitochondria; this enables ATP production in aerobic metabolism. When arterial oxygen tension (PaO_2) and consequently hemoglobin oxygen saturation (SaO_2) decrease, tissue oxygenation is impaired, anaerobic metabolism kicks in, lactic acidosis, organ dysfunction, and ultimately the risk of death increase. That means ensuring sufficient tissue oxygen delivery while accounting for variables like cardiac output, hemoglobin level, and oxygen saturation is the main objective of oxygen treatment.[3]

In clinical practice, the target peripheral oxygen saturation (SpO_2) range is maintained around 94-98% for most patients; this prevents both inadequate oxygenation and reduces the risks associated with excessive oxygen intake.[4,5] However, in patients at risk of chronic hypercapnia or CO_2 retention-such as those with chronic obstructive pulmonary disease (COPD)-the target saturation should be maintained within a lower range of 88-92%; This approach minimizes the risk of CO_2 retention and hypoventilation by disrupting the ventilation-perfusion (V/Q) balance.[5]

Additionally, the transport of oxygen to tissues depends not only on saturation but also on ventilation-perfusion matching, alveolar ventilation, and cardiac output. High oxygen concentration (high FiO_2) and excessive increases in arterial oxygen pressure can lead to oxygen toxicity, cellular damage in lung tissue, and inflammation by increasing the formation of reactive oxygen species (ROS)-therefore, dose adjustment (titration) and close monitoring are essential in oxygen therapy.[6,7]

In summary, oxygen therapy is essential for tissue metabolism, but it should be given by titration to reach the desired saturation range, following the maxim "neither too little nor too much"-considering the patient's physiological state, risk factors, and ventilation-perfusion status. This approach aims to minimize both the risk of hypoxia and the harm of hyperoxia; it is the physiological basis for the safe and effective use of oxygen therapy.[7]

CLINICAL INDICATIONS

Oxygen therapy is primarily administered to correct hypoxemia and is one of the first-line treatments in the management of many acute clinical conditions. Modern guidelines recommend avoiding both hypoxemia and hyperoxemia, and administering oxygen therapy titrated according to saturation targets (**Table 1**).[8]

Table 1. Practical guide to oxygen therapy in acute and critical illness

Clinical condition	Primary goal of oxygen therapy	Recommended SpO_2 target range	Preferred delivery method(s)	Key notes
Acute hypoxemic respiratory failure	Restore arterial oxygenation and prevent tissue hypoxia	92-96%	HFNO, NIV, face mask	Avoid hyperoxia; titrate according to PaO_2 and patient response
Sepsis and septic shock	Improve tissue oxygen delivery and reduce anaerobic metabolism	92-96%	Nasal cannula, HFNO, NIV	Liberal oxygen strategy has no mortality benefit; individualized titration required
Acute coronary syndromes	Prevent myocardial ischemia due to hypoxemia	Only if SpO_2 <90-92%	Nasal cannula	Routine oxygen for normoxemic ACS patients is not recommended
Trauma-related hypoxia	Prevent secondary brain injury and organ dysfunction	94-98%	HFNO, NIV, face mask	Avoid hyperoxia, especially in traumatic brain injury
Cardiogenic pulmonary edema	Improve gas exchange and reduce respiratory workload	94-98%	CPAP/BiPAP	NIV reduces intubation rates and improves clinical outcomes
COPD exacerbation	Correct hypoxemia while preventing CO_2 retention	88-92%	Venturi mask, nasal cannula	Over-oxygenation can cause hypercapnia due to hypoxic drive suppression
Peri-intubation oxygenation	Prevent desaturation during airway manipulation	≥92% pre-oxygenation	HFNO, NIV	HFNO/NIV reduces peri-intubation hypoxemia compared to standard face mask

Acute Hypoxemic Respiratory Failure

Acute hypoxemic respiratory failure can develop due to many causes, such as pneumonia, ARDS, pulmonary embolism, COVID-19 pneumonia, trauma, and postoperative complications. The primary goal of oxygen therapy in these patients is to provide adequate oxygenation while avoiding the potential harms of oxygen.[9] Current evidence shows that liberal oxygen strategies in ventilator-supported patients do not offer advantages over more conservative (controlled) oxygen strategies in terms of 28-90-day mortality and intensive care or intubation duration.[10]

Sepsis and Septic Shock

In sepsis and septic shock, tissue perfusion and oxygen delivery are impaired; therefore, oxygen therapy is an integral part of resuscitation. However, the superiority of a liberal oxygen approach over a conservative approach in critically ill patients has not been proven.[10,11] Oxygen therapy should be individualized based on the patient's hemodynamic status, oxygen demand, and target saturation.

Acute Coronary Syndromes

Although oxygen was routinely administered to patients with acute coronary syndrome (ACS) in the past, recent studies have shown that routine oxygen therapy is ineffective in patients with adequate oxygen saturation (SpO_2 ≥90%) and that excessive oxygen may even be contraindicated.[12] Therefore, it is recommended to avoid widespread oxygen administration in normoxemic ACS patients

Trauma-Related Hypoxia

Hypoxia resulting from causes such as thoracic trauma, lung contusion, hemothorax, pneumothorax, brain injury, or shock necessitates oxygen therapy in trauma patients.

Chapter 15

Carbapenems, Vancomycin, and Teicoplanin

Emine Sarcan

ABSTRACT

Carbapenems, vancomycin, and teicoplanin are critical antimicrobial agents widely used in the management of severe infections, particularly in emergency and critical care settings. The increasing prevalence of multidrug-resistant pathogens has heightened the importance of these antibiotics in contemporary clinical practice. Carbapenems represent broad-spectrum β-lactam antibiotics with potent activity against many Gram-negative organisms, including extended-spectrum β-lactamase–producing Enterobacterales, making them essential for the treatment of severe infections such as sepsis, complicated intra-abdominal infections, and hospital-acquired pneumonia. Glycopeptide antibiotics, including vancomycin and teicoplanin, remain key therapeutic options for serious Gram-positive infections, particularly those caused by methicillin-resistant Staphylococcus aureus. Their roles in emergency department management of life-threatening conditions such as septic shock, bacteremia, infective endocarditis, meningitis, and necrotizing soft tissue infections are discussed in detail. Additionally, considerations related to individualized dosing, renal function adjustment, adverse effects, and antimicrobial stewardship are highlighted. Understanding the pharmacologic and clinical characteristics of these agents is essential for optimizing therapeutic outcomes while minimizing toxicity and the development of antimicrobial resistance.

CARBAPENEMS

Introduction

Carbapenems represent a distinct subgroup of β-lactam antibiotics characterized by structural resilience against most extended-spectrum β-lactamases (ESBLs) and AmpC enzymes. Owing to their broad antibacterial coverage and pharmacodynamic robustness, they are frequently reserved for severe infections caused by multidrug-resistant (MDR) organisms, particularly in emergency and critical care settings.[1] These agents exhibit potent activity against Enterobacterales, anaerobes, and many Gram-positive pathogens, while meropenem and imipenem maintain activity against Pseudomonas aeruginosa (in contrast to ertapenem).[2] Their stability against hydrolysis by many β-lactamases is largely attributed to structural modifications at the C-1 position and the presence of a trans-1-hydroxyethyl side chain, which enhances resistance to enzymatic degradation.[3] Despite their therapeutic value, increasing global carbapenem use has accelerated the emergence of carbapenem-resistant Enterobacterales (CRE), posing a significant threat to antimicrobial stewardship programs and emergency department prescribing practices.[4]

Pharmacology Overview

Carbapenems exert bactericidal activity through high-affinity binding to multiple penicillin-binding proteins (PBPs), thereby inhibiting the transpeptidation step of peptidoglycan synthesis. This disruption compromises bacterial cell wall integrity, resulting in osmotic instability and cell lysis.[3] Pharmacodynamically, carbapenems demonstrate time-dependent killing, with clinical efficacy correlating with the duration that free drug concentrations remain above the minimum inhibitory concentration (fT>MIC). In critically ill patients, prolonged or extended infusion strategies have been associated with improved pharmacodynamic target attainment and potentially better clinical outcomes.[5]

Pharmacodynamics: Carbapenems are β-lactam antibiotics with bactericidal activity, and their primary mechanism of action is based on the inhibition of bacterial cell wall synthesis. These antibiotics bind with high affinity to penicillin-binding proteins (PBPs) located in the bacterial cell wall, thereby inhibiting peptidoglycan synthesis and leading to disruption of cell wall integrity. The process of bacterial cell lysis is associated with the activation of autolytic enzymes (autolysins) present in the cell wall. Following the binding of β-lactam antibiotics to PBPs, increased autolysin activity contributes to irreversible damage to cell wall integrity. In contrast, loss or suppression of the autolytic response has been reported to result in tolerance to β-lactam antibiotics, accompanied by a reduction in bactericidal activity.[1] The antibacterial activity of carbapenems is time-dependent, and clinical efficacy largely depends on the duration for which the free drug concentration stays higher than the minimum inhibitory concentration (MIC), expressed as fT>MIC. This pharmacodynamic characteristic necessitates appropriate dosing strategies and optimized dosing intervals, particularly in the treatment of severe infections.[1] This class of antibiotics exhibits potent activity against a broad spectrum of Gram-negative bacteria, as well as many anaerobic microorganisms and certain Gram-positive pathogens. Their strong binding affinity to PBPs and structural stability against numerous β-lactamase enzymes form the basis of their broad antibacterial spectrum. However, their activity is limited against MRSA, Enterococcus faecium, and certain intrinsically resistant pathogens.[2]

Pharmacokinetics:

Absorption: Carbapenems do not exhibit clinically significant oral absorption; therefore, therapeutic use requires parenteral administration, most commonly via the intravenous route. Following intravenous infusion, plasma concentrations rise rapidly. After a 500 mg dose of imipenem or meropenem, peak serum levels typically reach approximately 20-30 µg/mş. In contrast, ertapenem administered at 1 g achieves markedly higher peak concentrations, reflecting its distinct pharmacokinetic profile.[1]

Distribution: Carbapenems distribute primarily within the extracellular fluid space and penetrate effectively into most tissues and biological fluids. Meropenem demonstrates reliable cerebrospinal fluid penetration when the meninges are inflamed, which supports its use in central nervous system infections.[5] Imipenem and meropenem

Chapter 20

Somatostatin, Octreotide, and L-Ornithine / L-Aspartate

Fatma Selman

ABSTRACT

In human metabolism, a wide variety of peptides are produced in different regions of the body. One of these peptides is somatostatin, which has a cyclic structure. Somatostatin is widely distributed in neural tissues of the cortex, hypothalamus, brainstem, and spinal cord, as well as in paracrine and throughout the gastrointestinal system. Two distinct forms, somatostatin-14 and somatostatin-28, are secreted in various regions of the gastrointestinal system. Owing to these mechanisms, somatostatin and its analog octreotide are used therapeutically in numerous conditions, including gastrointestinal bleeding, pancreatic disorders, acute diarrheal diseases, hypoglycemia, and acromegaly. Ornithine and aspartate, located in another metabolic pathway, are endogenous peptides that play a crucial role in detoxification processes, in the liver, brain. The L-ornithine/L-aspartate (LOLA) preparation has been shown to be effective in hepatic encephalopathy by reducing blood ammonia levels.

SOMATOSTATIN ANALOGUES AND OCTREOTIDE

Introduction

Somatostatin and its analogues are important for gastrointestinal system. Subsequent studies revealed its involvement in multiple gastrointestinal processes. In addition, it is released from several regions of the nervous system.

Due to its widespread physiological effects, several synthetic analogues have been developed to enhance its clinical utility. These include octreotide, lanreotide, and pasireotide. The development of synthetic analogues has enabled their use in the treatment of hormone-secreting gastrointestinal tumors, portal hypertensive bleeding, and many other clinical conditions.[1,2]

Pharmacology Overview

Somatostatin-14 (S-14) and somatostatin-28 (S-28) result from post-translational processing of a prehormone. Somatostatin is a cyclic peptide, and the biological activity of both these peptids resides within the cyclic region of the mature peptide. The FWKT motif of the ring structure is essential for receptor binding, a discovery that facilitated the development of synthetic analogues such as octreotide. Octreotide has a significantly longer circulating half-life than native somatostatin.[3]

Somatostatin is predominantly present in neural tissues of the cortex, spinal cord and hypotalamus. It is also abundant in the gastrointestinal tract and pancreas, where it is produced by paracrine and endocrine-like D cells as well as enteric neurons. Both S-14 and S-28 are secreted throughout various regions of the gastrointestinal system.[1,2]

Somatostatin receptors are typical G-protein–coupled receptors, While these receptor subtypes do not differ in their binding affinity for somatostatin-14 or somatostatin-28, they show considerable variability in binding to synthetic somatostatin analogues. All somatostatin receptor subtypes are coupled to inhibitory G proteins, leading to reduced adenylate cyclase activity and decreased intracellular cAMP levels. Certain agonists may demonstrate functional selectivity at individual receptor subtypes, activating only specific receptor-mediated effects.

Somatostatin therapy can induce receptor desensitization and internalization within minutes, which may contribute to resistance during chronic treatment.[4]

The physiological actions of somatostatin are primarily inhibitory across multiple organ systems. In peripheral tissues, it suppresses both endocrine and exocrine secretion, reduces splanchnic blood flow, diminishes gastrointestinal motility, limits gallbladder contraction, and inhibits the release of numerous gastrointestinal hormones. Within the pancreatic islets, somatostatin exerts inhibitory effects on both α-cells and β-cells, thereby reducing glucagon and insulin secretion. In the central nervous system, somatostatin functions mainly as an inhibitory neuromodulator; however, depending on the specific neuronal circuits engaged, it may paradoxically stimulate certain endocrine pathways.[5]

Due to its very short half-life, the clinical use of native somatostatin is limited. In contrast, octreotide has a half-life exceeding 90 minutes, greater clinical stability, and more potent inhibitory effects while maintaining similar biological activity.[6]

Clinical Indications (General Use)

Somatostatin and its analogue octreotide have multiple clinical applications, including acromegaly, diarrhea, and gastrointestinal bleeding.

Acromegaly: Acromegaly results from excessive growth hormone secretion, most commonly due to a pituitary adenoma. Somatostatin analogues provide significant therapeutic benefit by suppressing hormone hypersecretion and reducing tumor-related symptoms, thus representing a key component of medical management.[7]

Inhibition of tumor growth: Somatostatin and its analogues are widely employed to limit the proliferation of neuroendocrine tumors. Their anticancer effects are mediated through somatostatin receptor activation, which modulates intracellular signaling pathways such as MAP kinase and phosphotyrosine phosphatases, ultimately leading to cell-cycle arrest or apoptosis.[8,9]

Diagnostic imaging: Many neuroendocrine tumors can be distinguished by the presence of somatostatin receptors on their cell surfaces. Somatostatin receptor scintigraphy is therefore used for tumor detection.[10]

Neuropathic pain: Neuropathic pain following nerve injury is often associated with increased activity of G-protein–coupled receptors and ion channels. Somatostatin analogues may exert analgesic effects in such patients. The widespread distribution of somatostatin receptors in the brain allows their use in migraine and cluster headache treatment.[11]

Chapter 25

Protamine Sulfate, Prothrombin Complex Concentrate, Tranexamic Acid

Burcu Doğan

ABSTRACT

Protamine sulfate, prothrombin complex concentrate, and tranexamic acid are important pharmacologic agents used in the emergency management of anticoagulation-related complications and major bleeding. Protamine sulfate reverses the anticoagulant effect of unfractionated heparin through ionic binding and formation of an inactive complex, although its effect on low–molecular-weight heparins is partial. Prothrombin complex concentrate, a plasma-derived preparation containing vitamin K–dependent clotting factors, enables rapid restoration of coagulation and is widely used for warfarin-associated major bleeding and urgent procedures, with potential off-label use in selected cases of direct oral anticoagulant–related bleeding when specific antidotes are unavailable. Tranexamic acid, a synthetic lysine analogue with antifibrinolytic properties, inhibits fibrinolysis and is commonly used to control major bleeding, particularly in trauma and selected mucosal hemorrhages. While these agents play a critical role in acute hemostatic management, their use requires careful consideration of dosing, timing, and potential adverse effects. This chapter summarizes the pharmacological properties, clinical indications, dosing strategies, and safety considerations of these agents, with particular emphasis on their use in emergency department practice.

PROTAMINE SULFATE

Introduction

Protamine is a small protein characterized by a high arginine content, with more than two-thirds of its amino acid composition consisting of arginine residues. The abundance of arginine residues gives protamine a strong positive charge, resulting in marked cationic and alkaline properties. Although protamine was historically extracted from salmon sperm, recombinant preparations are now also available.[1,2]

Protamine serves as the specific reversal agent for heparin and counteracts its anticoagulant activity by neutralizing its anti–factor Xa effects and can completely abolish its anticoagulant action. In contrast, the neutralizing capacity of protamine is reduced when low-molecular-weight heparins (LMWHs) are involved.

PHARMACOLOGY

Pharmacodynamics

Because of its high arginine content, protamine behaves as a strongly cationic molecule. When it encounters anionic unfractionated heparin, ionic binding occurs, leading to the formation of an inactive protamine–heparin complex. This complex lacks anticoagulant activity, thereby effectively neutralizing heparin.

For unfractionated heparin, this neutralizing effect is complete and occurs rapidly. In contrast, in the case of LMWHs, protamine fully neutralizes anti–factor IIa activity but only partially neutralizes anti–factor Xa activity. This partial neutralization is attributed to the weaker binding of protamine to the shorter polysaccharide chains characteristic of LMWHs.[3-5]

Residual anti–factor IIa and anti–factor Xa activity may become detectable again within approximately three hours after protamine administration.[6]

Pharmacokinetics

Protamine acts rapidly, typically neutralizing circulating heparin within about five minutes after administration. The elimination half-life of protamine is relatively short and is generally estimated to be between 7 and 10 minutes. The duration of effect is approximately 2 hours.[1,7]

While available evidence indicates that the heparin–protamine complex may undergo metabolism in the liver or kidneys, the precise metabolic pathway has not yet been clearly defined.[1]

CLINICAL INDICATIONS

Protamine is added to certain insulin formulations to prolong the duration of insulin action.

It is indicated for the reversal of excessive anticoagulant effects of unfractionated heparin and for the management of bleeding complications related to LMWHs.

In patients undergoing coronary artery bypass graft surgery, protamine is routinely used to reverse heparin anticoagulation and thereby decrease the risk of postoperative bleeding.

In patients requiring urgent surgical intervention, protamine allows prompt reversal of heparin-induced anticoagulation.

Protamine is also employed to antagonize the effects of heparin during dialysis, invasive vascular procedures, and in clinical situations such as acute ischemic stroke.

Clinical Indications in the Emergency Department

Within emergency medicine practice, protamine is primarily employed when rapid antagonism of heparin activity is required, such as in severe bleeding or before urgent procedures. However, it is ineffective for reversing anticoagulation caused by warfarin or direct oral anticoagulants (DOACs).

DOSING AND ADMINISTRATION

Protamine sulfate is typically administered intravenously (IV) through a peripheral line as a slow infusion lasting approximately 10–15 minutes. Protamine doses are summarized in **Table 1**.

Table 1. Protamine dosing table

Heparin type	Time	Protamine dose*	Amount of heparin	Notes
Unfractionated heparin	1-6 hours	1 mg	100 IU	If bleeding persists after 4 hours, protamine may be repeated at 0.5 mg per 100 units of heparin
Enoxaparin	3-12 hours	1 mg	1 mg	Protamine is not required if >12 hours elapsed since the last dose
Dalteparin		1 mg	100 IU	

*Pediatric dosing follows adult dosing principles

When administered within the first 1–6 hours following unfractionated heparin administration, protamine provides complete neutralization. The optimal dose for full reversal is determined according to the estimated amount of heparin remaining in the circulation. The remaining circulating heparin can be estimated according to the last administered dose, the time interval since administration, and the short elimination half-life of heparin (about 1–2 hours). For reversal, 1 mg of protamine is generally given per 100 units of heparin. When bleeding persists after four hours, supplemental protamine at 0.5 mg per 100 units of heparin may be considered.[8,9] The maximum single dose should not exceed 50 mg.[3]

For LMWHs, dosing recommendations vary by agent. If enoxaparin has been administered within the preceding 3–12 hours, protamine is given at a 1:1 ratio (1 mg protamine per 1 mg enoxaparin). For the neutralization of dalteparin, protamine is generally administered at a ratio of 1 mg per 100 units of dalteparin. If further reversal is indicated, a supplementary protamine dose of 0.5 mg may be considered. When more than 12 hours have elapsed since LMWH administration, protamine is generally not required.[9,10]

Renal impairment: Dose adjustment is generally not required; however, close clinical monitoring is recommended.

Hepatic impairment: Dose adjustment is generally not required; however, close clinical monitoring is recommended.

Pregnancy: Classified as category C and should be used during pregnancy only when the indication is clearly established and the potential benefit outweighs the risk.

Lactation: Evidence on the safety of protamine during lactation and its transfer into breast milk is currently lacking.

Pediatric dose: As in adults, the protamine dose in pediatric patients is adjusted according to the amount of heparin administered and is typically administered at 1 mg per 100 units of heparin, and the maximum recommended single dose is 50 mg. Recommended dosing based on the time elapsed since heparin administration is presented in **Table 2**.[11]

Elderly patients: Although no age-specific dose adjustment is recommended for protamine sulfate, elderly patients may be more vulnerable to hemodynamic instability and cardiopulmonary adverse events because of reduced physiological reserve and multiple comorbidities. Therefore, cautious dosing and slow IV administration are advised.

Antiepileptics

Merve Yazla

ABSTRACT

This chapter provides an evidence-based overview of antiepileptic drug use in the emergency department, focusing on the rapid and structured management of acute seizures and status epilepticus. A stepwise treatment approach is emphasized, highlighting the critical role of early benzodiazepine administration-particularly midazolam, given its rapid onset and versatile routes of delivery-as the first-line therapy. Second-line treatment options, including levetiracetam, fosphenytoin, and valproic acid, are discussed in detail, with attention to their pharmacological mechanisms, dosing strategies, safety profiles, and clinical considerations that guide individualized therapy. Levetiracetam is favored for its favorable pharmacokinetics and minimal drug interactions, while fosphenytoin offers improved tolerability compared to phenytoin, and valproic acid provides broad-spectrum efficacy with important safety considerations. The chapter also addresses the management of refractory status epilepticus, a life-threatening condition requiring escalation to continuous anesthetic infusions such as midazolam, propofol, or pentobarbital. Overall, this chapter integrates pharmacological principles with practical clinical guidance to support timely, effective, and safe seizure management in emergency settings.

FIRST-LINE THERAPY

Diazepam

Introduction: Diazepam is a long-acting benzodiazepine that has historically been a primary treatment for status epilepticus. Although its use in hospitals has been largely superseded by lorazepam due to its pharmacokinetic properties, it remains a crucial medication, especially in prehospital settings, due to its rapid onset and availability in various formulations, including rectal gel. This section covers the essential aspects of diazepam for emergency medicine practitioners.[1–2]

Diazepam, a long-acting benzodiazepine, rapidly crosses the blood-brain barrier but redistributes quickly, limiting anticonvulsant effect to 15-30 minutes. Concurrent long-acting therapy is essential.[2]

Pharmacology:

Pharmacodynamics: Diazepam potentiates gamma-aminobutyric acid (GABA) effects at the GABA-A receptor by increasing chloride channel opening frequency, leading to neuronal hyperpolarization and seizure suppression. [2]

Pharmacokinetics: Diazepam's high lipophilicity enables rapid central nervous system (CNS) penetration (onset <1 min IV) but causes quick redistribution to peripheral tissues, limiting anticonvulsant effect to 15-30 minutes. Hepatic metabolism via cytochrome P450 (CYP450) produces active metabolites (nordiazepam, oxazepam, temazepam), resulting in prolonged elimination (diazepam half-life [t½]: 20-50h; nordiazepam t½: 50-100h).[2]

Clinical indications:

- Status epilepticus (SE) and acute repetitive seizures
- Alcohol withdrawal syndrome
- Acute anxiety and panic disorders

Clinical indications in the emergency department:

- **SE:** Acceptable first-line alternative when lorazepam unavailable. Preferred for prehospital use via rectal route when IV access delayed. Requires concurrent long-acting anticonvulsant due to short duration (15-30 min).[1-3]
- **Alcohol withdrawal syndrome:** Long t½ prevents withdrawal seizures and manages autonomic hyperactivity.[1]
- **Acute anxiety and panic attacks:** Rapid anxiolysis for severe Emergency Department (ED) presentations.[1]

Dosing and administration:

Standard adult dose:

- **SE:** 5-10 mg IV (0.15 mg/kg), repeat every 5-10 min (max 30 mg).
- **CRITICAL:** Never exceed 5 mg/min infusion rate-risk of apnea, hypotension, and cardiac arrest.[2-3]

(Note: Full dosing details in **Table 1**)

Table 1. Diazepam dosing according to patient groups

Patient group	Recommended dose	Interval	Notes
Standard adult (SE)	5-10 mg IV (0.15 mg/kg)	Repeat every 5-10 min	Max 30 mg total, max rate 5 mg/min
Adult-alcohol withdrawal	10-20 mg IV/PO loading, then 5-10 mg		Symptom-triggered preferred
Pediatric (SE)	0.1-0.3 mg/kg IV/Rectal	Repeat once if needed	Max single dose 10 mg
Elderly	2-5 mg IV	Single or repeat once after 10-15 min	Max 10-15 mg total
Hepatic impairment (Child-Pugh B/C)	50% dose reduction	Extended intervals	Consider alternatives
Renal impairment (Severe)	Standard dose	Extended intervals if repeated	Monitor for metabolite accumulation

Chapter 37

Weaning from Mechanical Ventilation

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ABSTRACT

Mechanical ventilation is one of the fundamental life-sustaining supportive treatments in acute respiratory failure cases that develop in the emergency department, often due to reversible causes. However, unnecessary continuation of mechanical ventilation support after the primary pathology has been controlled is associated with significant morbidity and mortality causes such as ventilator-associated pneumonia, diaphragmatic dysfunction, prolonged hospital stay, and increased mortality. Therefore, timely and safe weaning from mechanical ventilation is considered a critical and multidimensional clinical decision-making process in emergency medicine practice. The weaning process requires a comprehensive approach that simultaneously assesses respiratory muscle function, gas exchange adequacy, cardiovascular stability, neurological status, and the level of control of the underlying pathology. Current evidence shows that decisions based solely on numerical ventilator parameters are not sufficient; integrated assessment of clinical stability, tolerance to spontaneous breathing trials, airway safety, and post-extubation support strategies significantly improves patient outcomes. This section addresses the weaning process from mechanical ventilation in the emergency department in light of current national and international guidelines, systematic reviews, and randomized controlled trials. Criteria for initiating weaning, methods for implementing spontaneous breathing trials, limitations of commonly used objective measures, and post-extubation management approaches, which are an integral part of a successful weaning process, are discussed in detail. In conclusion, the weaning process in the emergency department requires a patient-centered, physiology-based, and dynamic assessment. Weaning strategies initiated in a timely manner and based on a comprehensive clinical assessment contribute to improving patient prognosis by reducing unnecessary mechanical ventilation time and ventilator-associated complications.

INTRODUCTION

Mechanical ventilation is one of the fundamental life-sustaining supportive treatments in critical illness conditions that frequently develop in the emergency department due to reversible causes such as acute respiratory failure, sepsis, intoxication, and trauma.[1]

However, unnecessary continuation of mechanical ventilation support after the primary pathology has been controlled is associated with serious complications such as ventilator-associated pneumonia, diaphragmatic dysfunction, prolonged intensive care unit stay, and increased mortality.[2,3] Therefore, timely and safe weaning from mechanical ventilation is considered a critical clinical decision-making process in emergency medicine practice.

Weaning is the process of gradually reducing and discontinuing mechanical ventilation support after the patient's respiratory muscle strength, gas exchange capacity, and hemodynamic stability have returned to adequate levels.[4] Weaning attempts that are not performed at the appropriate time and using the appropriate method can lead to adverse clinical outcomes such as prolonged mechanical ventilation duration, the need for reintubation, ventilator-associated pneumonia, and increased mortality.[5] In this context, the systematic evaluation and effective management of the weaning process is of fundamental importance for patient safety and clinical outcomes in emergency department and intensive care settings.

THE CONCEPT AND CLASSIFICATION OF WEANING

Weaning is defined as the process of gradually separating the patient from mechanical ventilator support until they can spontaneously maintain adequate gas exchange and ventilatory effort. This process is not merely a technical application involving the reduction of ventilator settings; it is a multidisciplinary and complex clinical decision-making phase that involves the combined assessment of respiratory system functions, cardiovascular stability, neuromuscular status, and level of consciousness.[5,6]

Successful weaning is defined as the absence of the need for reinstituted invasive mechanical ventilation for at least 48 hours following extubation. Weaning failure encompasses the inability to tolerate a spontaneous breathing trial (SBT) or the need for reintubation within the first 48 hours after extubation. Weaning failure is associated with prolonged intensive care unit stay, increased ventilator-associated complications, and increased mortality rates.[5,7]

Weaning Classification

Current clinical classifications address the weaning process in three main groups: simple weaning, difficult weaning, and prolonged weaning. This classification improves clinical prediction and guides the individualization of weaning strategies.[8]

Simple weaning: Simple weaning refers to the patient tolerating their first spontaneous breathing attempt and the subsequent successful first extubation attempt. A significant proportion of patients receiving mechanical ventilation fall into this group, and they generally require minimal additional support.[9,10]

Difficult weaning: Difficult weaning refers to the patient's inability to tolerate the first SBT or the failure of the first extubation attempt, but the successful completion of extubation in subsequent attempts. In this patient group, diaphragmatic fatigue, cardiac reserve insufficiency, increased secretion load, and residual sedative effects are common clinical problems.[9,10]

Prolonged weaning: Prolonged weaning is defined as the patient experiencing at least three unsuccessful SBT attempts or requiring mechanical ventilation for 21 days or