Diplomarbeit

Acute Intoxications in Intensive Care Medicine: A Retrospective Data Analysis of an Internal Medicine Intensive Care Unit

eingereicht von

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zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde
(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Innere Medizin
Allgemeinen internistischen Intensivstation

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Graz, 15.09.2021

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Acknowledgements

I would like to extend my gratitude to my diploma thesis supervisors Priv.-Doz. OA Dr.med.univ. Dr.scient.med. Gerald Hackl and Univ. FA Dr.med.univ. Alexander Christian Reisinger. Without your constant support and extensive knowledge of intoxications and intensive care medicine, this thesis would not have been possible. Your insightful feedback and expansive statistical knowledge enabled me to write a diploma thesis I can be proud of.

Furthermore, I would like to thank my family and friends for their unwavering support, love and patience.

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Glossary and Abbreviations

5-HT	5-Hydroxytryptamine
AChE	Acetylcholinesterase
ALT	Alanine aminotransferase
APACHE IV	Acute physiology and chronic health evaluation
AST	Aspartate aminotransferase
CAMP	Cyclic adenosine monophosphate
CNS	Central nervous system
CO	Carbon Monoxide
CPR	Cardiopulmonary resuscitation
CYP2E1	Cytochrome P450 2E1
ECTR	Extracorporeal Treatment
Fe3+	Oxidized iron
GABA	Gamma amino-butyric acid
GBL	Gamma butyrolactone
GHB	Gamma hydroxybutyric acid
HBO	Hyperbaric Oxygenation
HCl	Hydrochloric Acid
HIET	High dose insulin euglycemic therapy
ICD	International classification of diseases
ICU	Intensive care unit
IQR	Interquartile range
M1	Muscarinic Receptor 1
M2	Muscarinic Receptor 2
M3	Muscarinic Receptor 3
M4	Muscarinic Receptor 4
MAO-I	Monoamine oxidase inhibitor
MARS	Molecular adsorbents recirculation system
MDMA	3,4-methylenedioxymethamphetamine
Met-Hb	Methemoglobin
mmHg	Unit millimeters of mercury
NAC	N-Acetylcysteine
NADPH	Nicotinamide-adenine-dinucleotide-phosphate

NAPQI	N-acetyl-P-benzo-quinone-imine
pH Value	Power of hydrogen value
QRS	Graphical deflections seen on electrocardiograms
QT	Graphical deflections seen on electrocardiograms
SERT	Serotonin transporter
SPSS	Statistical Package for Social Sciences
SSNRI	Selective serotonin noradrenalin reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor

Zusammenfassung

Hintergrund:

Schwere Intoxikationen nach der Ingestion, Inhalation oder intravenösen Applikation von Stoffen erfordern häufig eine intensivmedizinische Behandlung. Im Rahmen von Intoxikationen können unterschiedliche invasive Behandlungsschritte wie die Echtzeitüberwachung, Intubation, Beatmung und eine frühzeitige Giftelimination erforderlich sein, um körperliche Funktionen zu unterstützen bzw. zu ersetzen.

Ziel: Ziel dieser Diplomarbeit ist es Intoxikationen, die einen Intensivaufenthalt an der internistischen Intensivstation des Universitätsklinikum Graz erforderlich machen zu kategorisieren und die Verteilung der durchgeführten therapeutischen Schritte darzustellen.

Material und Methoden: Es wurden in dieser retrospektiven Datenanalyse toxikologische IntensivpatientInnen (n=227) von Jänner 2013 bis Dezember 2018 inkludiert. Die Patientenakten, sowie die intensivmedizinische Dokumentation im Computersystem wurden als Grundlage der Datenauswertung herangezogen. Es erfolgte die Einteilung der PatientInnen in neun unterschiedliche Gruppen je nach auslösenden Agens der Intoxikation (0= Unbekannt, 1= Äthanol, 2= Analgetika, 3= Antidepressiva, Antiepileptika und Antipsychotika, 4= Straßendrogen (inklusive Opiate, Kokain und Amphetamine), 5= Sedativa, 6= Kohlenmonoxid, Arsen und Zyanide, 7= andere nicht klassifizierbare Stoffe, 8= Mischintoxikationen von zwei oder mehr Stoffgruppen). Ebenfalls wurden die Intoxikationsfälle in Hinsicht auf das Geschlecht, der Altersverteilung, Grund für die Intoxikation, der primären und sekundären Giftelimination, Antidotgabe, Notwendigkeit für Intubation, Dauer der Intubation sowie Dauer des Intensivaufenthaltes und der Mortalität untersucht.

Ergebnis: Die häufigste Intoxikation beider Geschlechter, die eine intensivmedizinische Behandlung erforderlich machte, stellte die Gruppe der Mischintoxikationen dar. Bei den Frauen folgte die Gruppe der Antidepressiva, Antiepileptika und Antipychotika (17.5%), darauffolgend die Gruppe der anderen

nicht klassifizierbaren Intoxikationen (9.7%). Anschließend folgten Analgetika und Sedativa mit je 7.8% aller Intoxikationen. Bei den männlichen Intensivpatienten war die zweithäufigste Ursache für eine Intoxikation der Abusus von Straßendrogen (15.3%). gefolgt von Äthanol (12.1%), und Antidepressiva, Antiepileptika und Antipsychotika (9.7%). 52% aller Intoxikationen waren in suizidaler Absicht, ein Viertel aufgrund von rekreationellen Gründen, und 13.2% der Intoxikationen waren akzidentiell. Ein Viertel aller PatientInnen erhielten Aktivkohle als primäre Giftelimination und bei 6.6% wurden sekundäre Gifteliminationsmaßnahmen durchgeführt. Frauen erhielten signifikant öfter primäre Gifteliminationsmaßnahmen (p=0.008). Vier Prozent aller toxikologischen PatientInnen verstarben während des ICU-Aufenthalts.

Zusammenfassung: In dieser retrospektiven Datenanalyse konnten die häufigsten Intoxikationen auf der internistischen Intensivstation, als auch die notwendigen therapeutischen Maßnahmen erstmalig aufgeschlüsselt und mit der internationale Datenlage verglichen werden.

Abstract

Background: Intoxications following ingestion, inhalation or intravenous application of substances can require treatment in an intensive care unit (ICU). Reduced states of consciousness or impaired organ function, invasive therapeutical measures such as intubation, mechanical ventilation, monitoring and toxin elimination may be necessary.

Objective: The aim of this diploma thesis is to categorize intoxications that required a stay at the medical intensive care unit at the University Hospital Graz and to analyze the distribution of necessary therapeutical measures.

Material and Methods: In this retrospective data analysis, ICU patients (n=227) from January 2013 until December 2018 were included. Patient files and electronic documentation were utilized for data collection. Patients were separated into nine groups according to the causational substance (0= unknown, 1= ethanol, 2= analgesics, 3= antidepressants, antiepileptics and antipsychotics, 4= street drugs including opiates, cocaine and amphetamines, 5= sedatives, 6= carbon monoxide, arsenic and cyanide, 7= other not categorized substances and 8= combined drug intoxications of two or more substance groups). Intoxications were analyzed according to the distribution of sex, age, reason for intoxication, toxin elimination, antidotes administered, intubation, as well as length of the ICU stay and ICU mortality.

Results: Combined drug intoxications are the most common intoxication requiring intensive care treatment. In females, this was followed by the group of antidepressants, antiepileptics and antipsychotics (17.5%), and the group “other” (9.7%). Analgesics, sedatives and ethanol were almost equally common at 5-8%. In males, following the combined drug intoxications, the most common singular substance intoxication were street drugs (15.3%), followed by ethanol (12.1%), and the group of antidepressants, antiepileptics and antipsychotics (9.7%). Approximately half of all intoxications were intended suicide. One quarter of

patients received activated charcoal as primary detoxification and 6.6% of patients required secondary detoxification methods. In addition, females received primary detoxification methods significantly more often than males (p=0.008). ICU mortality regarding intoxication patients was low at 4%.

Conclusion: In this retrospective data analysis, the distribution of the most common intoxications leading to a stay at the medical intensive care unit and the necessary therapeutical steps, as well as ICU mortality were determined and compared to international data.

1 Introduction

1.1. Epidemiology

Acute intoxications following the inhalation, ingestion or intravenous administration of substances are a frequent cause for admission to medical intensive care units (ICU) worldwide. Considering the varying capacities of comprehensive patient monitoring and resources, 3.7-40% of patients with acute intoxications in the emergency department are admitted to the ICU (1, 2). As a result, it has become increasingly important to focus on and categorize the most common substances and the necessary therapeutical measures. This allows for early targeted diagnostics, treatment protocols to be established and to enable strategic planning of intensive care bed capacities.

Patients requiring intensive care measures or observance can present to an ICU in varying severity. Multiple studies have shown that the mortality rate of these patients is surprisingly low at 1.9- 2.1% (1, 3). In addition, according to a study done by Heyerdal et al., 58% of patients had an ICU stay of one day, two days were necessary for 31% of patients, and only 11% stayed three or more days (4). Taking the international data into account, it was of increasing importance to assess and compare patient data of the medical intensive care unit in Graz to international standards.

This diploma thesis offers a structured overview of common intoxications, pathophysiological mechanisms, and therapeutic options, as well as an insight into the substances present in patients with acute intoxications that are admitted to an intensive care unit. Furthermore, utilizing retrospective data analysis, the median length of stay, necessary therapeutical steps, and mortality rate at the intensive care unit of the Department of Internal Medicine, University Hospital Graz were evaluated.

1.2. Toxidromes

The classification of patient symptoms following acute intoxications in groups according to toxidromes, or toxic syndromes, can aid in establishing a correct and rapid diagnosis, thus enabling early specialized treatment including detoxification and the application of antidotes. The initial diagnostic criteria in patients to evaluate the presenting toxidrome are a complete physical examination, monitorization of the patient including pulse oximetry, invasive or noninvasive blood pressure monitoring, a 12-lead electrocardiogram, laboratory blood tests, blood gas analysis, end tidal carbon dioxide monitoring and urine samples (5, 6). Consequently, this grouping of typical symptoms can aid in the identification of intoxications and lead to early initiation of adequate treatment. There are six main toxidromes commonly described in literature, namely, sedative hypnotic, opioid, sympathomimetic, anticholinergic, cholinergic, and neuroleptic agent toxidromes (7, 8). In recent years, a seventh syndrome, namely the serotonergic toxidrome has been increasingly mentioned in literature (9).

Toxidromes enable a rapid conclusion to be drawn when a singular substance is ingested. Nevertheless, there are some limitations to this method of classification (6). An intoxication with more than one substance or substance groups can produce a complex symptom combination and interfere in the correct diagnostic processes. In addition, a plethora of new medications and designer drugs do not typically conform to the diagnostic criteria or can result in similar symptoms to other substances with different pathophysiology, and therefore requiring different treatment. Furthermore, it is important to note that a singular focus on toxidromes can limit differential diagnostic thinking and could result in underlying non toxicological diseases being overlooked.

1.2.1. Sedative/Hypnotic Toxidrome

The sedative hypnotic toxidrome is commonly caused by substances such as benzodiazepines, ethanol, barbiturates, gamma hydroxybutyrate (GHB) and gamma butyrolactone (GBL) (9, 10). Typical symptoms of the sedative hypnotic toxidrome are depression of the central nervous system, hyporeflexia, intact respiratory drive or minimal bradypnea, regular pupil size and possible hypotension (9).

These symptoms can be explained when considering the pharmacology of benzodiazepine and barbiturate interaction. Gamma-aminobutyric acid (GABA) functions as an inhibitory neurotransmitter in the central nervous system (CNS). Benzodiazepines serve as GABA-A receptor modulators and bind to the GABA-A receptors, which contain ligand-gated chloride ion channels (11). This bond facilitates a conformational change of the receptor, resulting in an increased frequency and duration of chloride transport into the cell (11). Consequently, when GABA is present, cells are hyperpolarized and exert inhibitory effects on the central nervous system (12).

Similarly, barbiturates also increase the inhibitory effect of GABA via GABA-A receptor modulation by prolonging the chloride channel influx into central nervous cells. Barbiturates applied in high doses, in comparison to benzodiazepines, can activate chloride channels directly (13). Consequently, barbiturates can activate the inhibitory pathway in absence of GABA, and also increase the chloride channel influx more significantly than benzodiazepines (13). This difference in the mechanism of action explains the increased symptom severity of a high dose barbiturate intoxication in comparison to a high dose benzodiazepine intoxication (13).

GHB is a recreational drug colloquially known as the “date rape drug” or is also commonly referred to as liquid ecstasy. A structurally similar pro-drug known as GBL can also be utilized as a recreational drug, as it is rapidly converted into GHB. GHB functions as a depressant of the central nervous system by interacting with the GABA-B receptor, in comparison to other common sedative agents, which act on the GABA-A Receptor (14).

Furthermore, unique pharmacological aspects of GBL/GHB intoxications must be considered. The maximum concentration of GHB in the bloodstream, occurs rapidly, at around 20-40 minutes after ingestion (14). Similarly, the half-life of GHB is short at approximately 30-50 minutes after ingestion (14). Consequently, the range of detection in the bloodstream is limited to approximately 4-5 hours after application and 8-10 hours in urine samples (14).

Ethanol is the most widely utilized sedative/hypnotic agent, due to its wide availability and social context. Therefore, severe misuse and abuse of alcohol has become a common reason for admission to the intensive care unit (15). Ethanol’s pathophysiological effects on the central nervous system are still object of considerable research. Studies have, however, come to the conclusion that ethanol and its metabolites function via a plethora of pathways, one of which, being on subunits of the GABA-A receptor (16). Ethanol binds to GABA-A receptors, consequently causing a chloride influx and hyperpolarizing cells of the central nervous system (16). This GABA mediated effect can result in significant central nervous depression when consumed in high doses (17).

1.2.2. Opioid Toxidrome

Common synthetic and naturally occurring opioids such as hydromorphone, oxycodone, dihydrocodeine, fentanyl, morphine and heroin can result in profound analgesia and sedation, but also cardiorespiratory depression. Typical symptoms of an acute opioid toxidrome are severe respiratory depression with bradypnea resulting in hypoxia, as well as miosis, analgesia, coma, hypotension, bradycardia,

nausea and reduced gastrointestinal motility (18). In addition, pulmonary edema can occur in opioid intoxication (18). Rhabdomyolysis and critical limb ischemia caused by prolonged muscle compression, hypoxic brain and renal damage are common delayed effects of opioid intoxication due to significant hypoxic organ injury (9). The severe depressant effect of opioids on vital bodily functions, especially in high doses, result in a grave increase in mortality and morbidity in comparison to other substance groups (9).

There are three common opioid receptors types, which are located primarily in the neural cells of the central nervous system: μ-opioid receptor, the δ-opioid receptor and the κ-opioid receptor (19). The μ-opioid receptor plays a central role in pain inhibition, resulting in the profound analgesic effect of opioids, but also in the symptoms of acute opioid intoxications. Following the application of an opioid, G-Protein coupled receptor pathways are activated, causing a decrease in adenylyl cyclase function. This results in lower intracellular cyclic adenosine monophosphate (cAMP) levels, consequently hyperpolarizing cells and causing reduced neurotransmitter release (19). Additionally, the effects of opioids are not limited to the central nervous system, as opioid receptors are located throughout the body and commonly exert their effects on the gastrointestinal tract resulting in reduced motility (19).

The severe effect of opioids on the respiratory and circulatory system, consequently cause the necessity of an aggressive intensive care treatment plan to adequately treat organ dysfunction caused by prolonged hypoxia and ischemia. Due to the oftentimes delayed medical care of intoxicated patients and prolonged phases of coma; rhabdomyolysis, compartment syndrome, and acute kidney injury are common (9). Similarly, prolonged phases of hypoventilation can result in irreversible hypoxic brain injury (9).

1.2.3. Sympathomimetic Toxidrome

The sympathomimetic toxidrome is typically characterized by increased activation of the sympathetic nervous system. Common causational substances of the sympathomimetic toxidrome include cocaine, amphetamines and methamphetamines, ketamine and a plethora of new designer stimulants. Patients suffering from a sympathomimetic toxidrome can present with tachycardia, bronchodilation, tachypnea, mydriatic pupils, reduced bowel and urinary function, severe neurological agitation, paranoia, psychotic symptoms and seizures (9). Typical cardiac complications of severe sympathomimetic intoxications are palpitations, arrhythmias, hypertension, and ischemia (9).

Cocaine inhibits the reuptake of catecholamines in the synaptic cleft, causing an activation of the sympathetic nervous system due to alpha adrenergic activation and an increased sensitivity to noradrenaline (20). This results in the typical symptoms of tachycardia and high blood pressure, resulting in an increase in myocardial oxygen demand (20).

Furthermore, cocaine can cause vasospasm of the coronary arteries due to increased endothelin-1 secretion and thrombosis by modulating platelet function (21). This mismatch of decreased oxygen supply and increased oxygen demand can in turn cause myocardial ischemia in otherwise healthy patients (20). In addition, cocaine also acts on myocardial cells as a class I antiarrhythmic agent and local anesthetic, causing significant arrythmia and electrocardiographic abnormalities including QRS and QT interval prolongation (20).

Amphetamines (e.g. speed), methamphetamines (crystal meth) and MDMA (3,4-methylenedioxymethamphetamine, Ecstasy) are stimulants that can also cause a sympathomimetic toxidrome (22). Amphetamines exert their primary effect in the central nervous system at the noradrenaline transporter, by causing an increased secretion of noradrenalin into the extracellular space (22). In addition, amphetamines modulate the reuptake of several other presynaptic monoamine

transporters, such as the serotonin (SERT) and dopamine transporters, which results in increased concentrations of neurotransmitters in the synaptic cleft (22).

Similar to other sympathomimetic drugs, amphetamines can lead to euphoria, increased activity, anxiety, paranoia, hallucinations, tachycardia, high blood pressure, hyperthermia, and a reduction of appetite (22). Considering the symptoms of the sympathomimetic toxidrome the most common uses for these substances becomes evident, namely, doping, weight loss and as a party drug.

1.2.4. Anticholinergic Toxidrome

A variety of commonly prescribed medications function via anticholinergic pathways. These include, but are not limited to: antipsychotics, antihistamines, muscle relaxants, atropine and Parkinson medications. These substances function as competitive antagonists of acetylcholine at peripheral and central muscarinic receptors, resulting in an inhibition of typical cholinergic activity such as cognitive functioning (23). Inhibition of the M1 receptor in the central nervous system results in the typically observed altered mental status and agitated delirium in anticholinergic intoxications (23). Other symptoms of the anticholinergic toxidrome are mediated mainly by the M2, M3 and M4 receptors (23).

Symptoms of an intoxication with anticholinergic substances include altered mental status such as delirium or hallucinations, mydriasis, hyperthermia, vasodilatation, anhidrosis and tachycardia (9). Further symptoms can include but are not limited to urinary retention, decreased bowel motility, tremor, seizures, and coma. The typical mnemonic “hot as a hare” (hyperthermia), “red as a beet” (flushed skin), “blind as a bat” (mydriasis), “dry as a bone” (dry skin and mucosa) and “mad as a hatter” (delirium) can be utilized to characterize the anticholinergic toxidrome (24). Moreover, it is vital to consider that symptom onset and the severity of symptoms can be prolonged, due to anticholinergic effects resulting in reduced gastrointestinal motility, possibly delaying the absorption of the causational substance (9).

1.2.5. Cholinergic Toxidrome

The cholinergic toxidrome is rare in Austria, but can be caused by pesticides such as organophosphates or carbamates, an overdose of cholinesterase inhibitors or the use of sarin as a chemical weapon (9). The method of action is primarily an inhibition of the enzyme cholinesterase, causing reduced hydrolysis of acetylcholine and consequent accumulation of acetylcholine in the synaptic cleft (25). As a result, muscarinic and nicotinic acetylcholine receptors are activated and cholinergic transmission significantly increases (26).

A complex combination of muscarinic and nicotinic activation occur in the cholinergic toxidrome. Muscarinic pathways cause symptoms such as sweating, salivation, bronchospasm, bronchorrhea, diarrhea, vomiting, miosis, bradycardia and hypotension (27). Symptoms typical for nicotinic activation include tachycardia, muscle weakness, paralysis, and coma (27).

1.2.6. Serotonergic Toxidrome

Serotonin syndrome is caused by an overdose consisting of selective serotonin reuptake inhibitors (SSRI's) or selective serotonin noradrenalin reuptake inhibitors (SSNRI's) commonly utilized in the treatment of depression. The combination of serotonergic substances with monoamine oxidase inhibitors (MAO-I) or tramadol have also been reported to generate serotonergic symptoms (28). The serotonergic toxidrome following medication intake is a relatively new phenomenon, as SSRI antidepressant prescription has shown an 18% increase in cases in the U.S. from 2002 to 2016 (28).

SSRI's have a broad method of action by altering the typical serotonin pathways in the central and peripheral nervous system. 5-Hydroxytryptamine (5-HT), also known as serotonin, is a neurotransmitter with central receptor functions regulating affective behavior, appetite, thermoregulation, motor tone and gastrointestinal regulation (28). SSRI's function by inhibiting serotonin reuptake from the synaptic cleft and further modulate postsynaptic serotonin receptors (28).

As a result serotonergic activation is increased, mainly via the 5-HT1a and 5-HT2a receptors (28). Serotonin noradrenaline reuptake inhibitors also exert their effect through the interaction with 5-HT receptors, yet also act by reducing the reuptake of noradrenaline in the synaptic cleft, with the intended effect of increasing activation of the sympathetic nervous system (29). In intoxications with serotonin noradrenaline reuptake inhibitors, symptoms such as an increased activation of the sympathetic nervous system can also be expected (29).

Typical symptoms of increased serotonergic activity include neuromuscular activation and muscle rigidity, hyperreflexia, agitation, delirium, hyperthermia, seizures and metabolic acidosis (9). Differentiation of serotonergic from an anticholinergic syndrome is oftentimes difficult and requires careful observation of patient symptoms and past medical history. Gastrointestinal function can aid in this difficult distinction, as diarrhea can typically be observed in the serotonergic toxidrome, whereas gastrointestinal motility is reduced in anticholinergic toxidromes (9). Similarly, diaphoresis is observed in serotonergic toxidromes, and is typically reduced in the anticholinergic toxidrome (9).

1.3. ICU Treatment of Patients with Acute Intoxications

1.3.1. Primary Toxin Elimination

Primary toxin elimination involves the removal of a toxic agent from the body, before it is absorbed, therefore aiming to prevent systemic effects on the patient. Historically, multiple methods of toxin removal such as the implementation of ipecac syrup, gastric lavage and whole bowel irrigation have been utilized. As these have become increasingly obsolete, activated charcoal has taken up a key role in a variety of acute poisonings (30, 31).

1.3.1.1 Activated Charcoal

Activated charcoal can be specifically utilized in the initial one to two hours following the ingestion of a toxic substance amount (32). Nevertheless, delayed or repeated clinical implementation for specific intoxications have been described as effective in literature (33). Especially patients with intoxications of medications with delayed release coatings, or substances that take part in the enterohepatic circulation pathway, may benefit from activated charcoal being administered in the first six hours or repetitive application (33). Furthermore, ingestion of potential lethal doses of substances without specific antidotes may be an indication for activated charcoal outside the initial 1-2 hour period.

Activated charcoal can bind significant amounts of toxins and drugs in the gastrointestinal tract, due to its large surface area and chemical composition (33). Once administered orally or through a nasogastric tube, it binds to the toxic substance, prevents its adsorption in the small intestine and the toxin is then excreted with the stool (33).

It is of utmost importance for the therapeutical efficacy following the application of charcoal, that the causational substance was taken orally, has chemical properties that allow it to be adsorbed by charcoal or has a significant enterohepatic circulation (33). Some substances such as alcohols, inorganic salts, metals such as lithium, acids and bases and solvents cannot bind to activated charcoal and its use is therefore not indicated (33).

Furthermore, a prerequisite for the intake of activated charcoal is that the patient must be conscious, cooperative and able to swallow effectively, e.g. unaltered protective reflexes. Alternatively airway protection of comatose patients with intubation should be considered, in which case activated charcoal can be applied utilizing a nasogastric tube (33).

Oftentimes a significant limitation of activated charcoal is the danger of application in patients with an altered mental status, that do not fulfill intubation criteria. In these cases, the risk of charcoal lung aspiration, and also the risks of intubation must be weighed against the benefit of reducing potentially life threatening substance absorption.

The recommended dosage of activated charcoal is adapted to patient body weight and should be 0.5 -1 gram per kilogram body weight, however, in adult patients it is common practice to apply a single dose of 50 grams in a water suspension, if they do not qualify for repeated doses (33).

1.3.1.2 Gastric Lavage

Gastric lavage is a method of primary detoxification, in which fluid is introduced via an orogastric tube and the stomach contents are consequently aspirated, with the aim of removing the toxic substance. There is little data suggesting that gastric lavage has any patient benefit and the risk of pulmonary aspiration of gastric contents without intubation is high (30). Its application has therefore become increasingly rare and should only be executed in special circumstances after expert consultation (30).

1.3.1.3 Whole Bowel Irrigation

Whole bowel irrigation is an increasingly rare procedure where a polyethylene glycol electrolyte solution is enterally applied, causing liquid bowel movements and consequently rapid removal of ingested substances from the gastrointestinal tract (34). In cases of the ingestion of delayed-release coated medications, especially two hours or more after ingestion or in cases of body packing, whole bowel irrigation can be considered (34). Nevertheless, there is no empirical data to indicate that whole bowel irrigation improves patient outcome and is therefore not established in routine practice (35).

1.3.1.4 Ipecac Syrup

Ipecac syrup can be utilized to induce vomiting, with the goal of removing the intoxicating substance. Ipecac syrup interacts with the stomach lining, while also inducing emesis via interactions in the central nervous system (36). As a result, it facilitates toxic substance removal through emesis. According to literature, ipecac syrup should not be utilized in medical practice, as it reduces the effectiveness of other toxin elimination or reversal treatments (31).

1.3.1.5 Endoscopic Medication Retrieval

Following the ingestion of a large amount of pills, some patients on a case to case basis may benefit from an endoscopic medication retrieval. Pharmacobezoars are a complex mass of medication, their coating and binding substances, which conglomerate in the stomach resulting in delayed or hindered gastric passage. Consequently, the medications cannot be excreted with the stool, and its intoxication window can be prolonged (37). There are only singular case reports regarding the evidence of endoscopic medication retrieval, but it has been reported in intoxications following the ingestion of slow release clomipramine (38), extended release potassium chloride (39), lithium (40), and extended release quetiapine (41). In intoxications with few other treatment options and hindered gastric passage, endoscopic retrieval of the medication masses was utilized and deemed feasible.

1.3.2. Secondary Toxin Elimination

1.3.2.1 Extracorporeal Toxin Elimination

Extracorporeal toxin elimination or extracorporeal treatment (ECTR) is a method of toxin removal in severe intoxication cases, by method of hemodialysis, hemofiltration, hemoperfusion, and molecular adsorbent recirculating systems (MARS). These ECTR techniques are common in intensive care units and require large vascular access, close patient monitoring and specialist teams.

Hemodialysis is a method of renal replacement therapy, which allows intensive care specialists to precisely influence toxin elimination, electrolyte and pH values. In cases of severe intoxication, either caused by, or resulting in impaired kidney function, or if the clinical evaluation concurs that there are limited treatment options, then dialysis can be indicated. Hemodialysis functions by an exchange of substances by diffusion along a concentration gradient of a semi-permeable membrane (42). As a result, toxic substances, but also water and electrolytes can be removed from the body, bypassing the kidney and allowing for adequate patient fluid balance (42). Criteria for successful treatment of intoxications utilizing hemodialysis include water-solubility, low molecular weight and low protein-binding tendencies (42). Depending on the intended substance, membranes or flow rates can vary to enable optimal toxin removal (42).

Hemoperfusion is a method of blood filtration to remove substances of larger molecular size or higher protein binding tendencies, as these cannot be adequately removed by hemodialysis (43). Blood passes through an external filter consisting of sorbent material, resulting in specific toxins and waste products binding to the filter material, whereas blood cells can pass through the membrane (43). It can be utilized in intoxications including theophylline, phenytoin, phenobarbital, carbamazepine, and paraquat (43). A considerable limitation of hemoperfusion is that electrolyte or acid-base dysregulation and fluid balancing cannot be achieved with hemoperfusion (43).

Other methods that can be utilized in select cases are hemofiltration or a molecular adsorbent recirculating system (MARS). Hemofiltration utilizes convection by applying a transmembrane pressure to continuously remove plasma by ultrafiltration (42). In addition, MARS can be indicated in intoxications with substances that have albumin-binding tendencies such as paracetamol or mushroom poisonings (44).

1.3.2.2 Hyperbaric Oxygenation Therapy

Hyperbaric oxygenation (HBO) therapy is the treatment of exposing a patient to 100% oxygen in a hyperbaric chamber with a surrounding pressure of ≥ 2 bar (45). Physiologically at normal atmospheric pressure, the body's oxygenation occurs by the binding of oxygen to hemoglobin and its consequent delivery to organs and tissues (45).

When higher external pressure (alveolar oxygen partial pressure) is applied, oxygen can be increasingly dissolved in the bloodstream according to Henry's law (45). At high alveolar oxygen partial pressures (2000mmHg), enough oxygen can theoretically be dissolved in the bloodstream to enable oxygenation of bodily tissues completely without hemoglobin (45).

Carbon monoxide (CO) has an around 300 times higher affinity to hemoglobin than oxygen. In patients with carbon monoxide poisoning, oxygen is displaced from its erythrocyte binding site, and CO furthermore functions as an inhibitor of cytochrome-oxidase in the respiratory chain (45). Consequently causing severe hypoxia resulting in symptoms such as dizziness, headaches, blurred vision, emesis, convulsions, reduced mental status, coma and death (46).

The treatment of CO intoxications includes high flow oxygen therapy and rapid hyperbaric oxygenation therapy. HBO results in a competitive displacement of CO by oxygen and a reduction of the half-life of carbon monoxide bound hemoglobin from 4 to 6 hours in ambient air conditions, to under thirty minutes, resulting in rapid disassociation and elimination of CO (46).

1.3.2.3 Lipid Rescue Therapy

Lipid rescue therapy consists of the intravenous application of a lipid emulsion, commonly intralipid 20%, in local anesthetics systemic toxicity or substances with lipophilic traits (47). Research has also indicated a use for lipid emulsion therapy in severe intoxications with lipophilic antiarrhythmic medications such as beta blockers and calcium channel blockers, as well as intoxications with tricyclic antidepressants (47). In severe intoxications resulting in extreme cardiorespiratory compromise following the application or ingestion of lipophilic substances, lipid emulsion therapy should be considered (47).

1.3.2.4 High Dose Insulin Euglycemic Therapy

High dose insulin euglycemic therapy (HIET) can be utilized in severe calcium channel and beta blocker intoxications (48). Intoxications with antiarrhythmic and antihypertensive medications can result in cardiotoxic effects presenting with symptoms such as bradycardia, hypotension, and cardiogenic shock (48).

Calcium channel blockers act on cardiac L-type voltage-gated calcium channels, as well as vascular calcium channels (48). Following symptomatic treatment of calcium channel blocker intoxications such as volume repletion and the implementation of catecholamines, high dose insulin and glucose therapy can be utilized (49). More research needs to be done to fully understand the pathophysiological mechanism leading to blood pressure stability following HIET. Its suspected method of action is by increasing contractility of smooth muscle, following adequate glucose adsorption and availability resulting in increased cardiac function and consequent cardiopulmonary stabilization (49).

1.3.2.5 Urine alkalization

Urine alkalization is a method of secondary detoxification with the aim of increasing the elimination of substances such as methotrexate, phenobarbital and salicylates, without necessarily increasing general diuresis rates (50).

The intravenous application of alkaline substances such as sodium bicarbonate, aims in producing urine with a pH of 7.5 or higher, resulting in ionization of weak acids and increased elimination of the toxic substances with the urine (51). In severe salicylate poisoning, where dialysis is not indicated, urine alkalization should be utilized as the first line of therapy (50).

1.3.2.6 Forced diuresis

Forced diuresis is generally considered to be an intended increase in diuresis by utilizing isotone intravenous drips and diuretics. Due to an increase in diuresis, renal clearance of the intoxicating substance is anticipated. There are few case reports and no standardized procedure for this method of secondary elimination and more studies would be necessary, to determine its use in acute toxicological patients.

1.4 Antidotes and Antagonists

1.4.1 Naloxone

Naloxone is utilized to reverse the cardiopulmonary and central nervous depression caused by opioids. Its method of function is a competitive opioid antagonism blocking the binding site of opioids (52). Intravenous application results in a rapid onset of action in under one to two minutes. The suggested dosage varies in literature and common practice has shown that naloxone should be titrated according to the patients level of consciousness and symptoms (52).

Typical doses in adults to are 0,1 -0,4 milligrams intravenously at a slow rate with repeated application until the desired effect is achieved (52). If no change in vigilance and breathing rate is observed following high doses of naloxone, then an alternative diagnosis must be considered (52). In addition, pulmonary aspiration of gastric contents should be considered and ruled out before application of naloxone, as endotracheal intubation and anesthesia may be indicated instead.

The duration of action of naloxone is around 20-90 minutes and the patient must be observed carefully, to prevent a repeated opioid toxidrome as the naloxone wears off (52). Continuous application of naloxone via an infusion pump may be necessary in high dose intoxications. Furthermore, intranasal and intramuscular naloxone application has become increasingly utilized in recent years, in response to the United States opioid crisis (53).

1.4.2 Flumazenil

Flumazenil is an antidote utilized to reverse the effects of a benzodiazepine overdose. Flumazenil is also a competitive receptor antagonist, as it blocks the GABA-A binding site of benzodiazepines, resulting in a decrease of chloride influx into the cell leading to a reversal of the sedative hypnotic effect (52).

The suggested method of application is intravenously with an initial dosage of 0.1 milligrams per minute, repeated until the desired clinical effect is observed. Similarly to naloxone, the intravenous onset of action is rapid at around 1-2 minutes and a possible pulmonary aspiration of gastric contents should be considered before application (52). The elimination half-life time of flumazenil is around 60 minutes and therefore patients must be monitored closely to prevent a repeated sedative/hypnotic toxidrome, due to residual benzodiazepines present in the patients tissue and blood stream (52).

Furthermore, it has become evident that combined drug intoxications of benzodiazepines and tricyclic antidepressants should not be reversed with flumazenil, as benzodiazepines protect patients from adverse effects such as convulsions in tricyclic intoxication (54).

1.4.3 Physostigmine

Physostigmine is utilized as an antidote in intoxications presenting as anticholinergic toxidromes. It functions as an indirect parasympathomimetic by inhibiting acetylcholinesterase (AChE), an enzyme that breaks down acetylcholine in the synaptic cleft (23). Consequently, this results in an accumulation of available acetylcholine to competitively bind to muscarinic receptors. The anticholinergic substance is therefore increasingly displaced from the receptors and a decrease in anticholinergic symptoms can be observed (23). Furthermore, physostigmine can pass the blood brain barrier and therefore can exert its therapeutical effect in central nervous anticholinergic, as well as peripheral symptoms of the intoxication (23).

The suggested i.v. dose is a slow application of 0.04 mg/kg at a maximum application rate of 1mg per minute and a maximum of 2 mg per application. The total dosage of applied physostigmine should be titrated following the patient's clinical response. Repeated application following insufficient patient response can be considered after 5-20 minutes. In addition, it is vital to consider that the elimination half-life of physostigmine is extremely short at 22 minutes after intravenous bolus application (23). Consequently, continuous application with an infusion pump may be necessary.

1.4.4 N- Acetylcysteine

N-Acetylcysteine (NAC) is utilized as the standard method of treatment in intoxications of acetaminophen, commonly known as Paracetamol. Paracetamol has become a commonplace over the counter analgesic and antipyretic. When consumed in large amounts, the regular metabolization process is oversaturated and the co-substrate glutathione, which aids in metabolization of acetaminophen to non-toxic end products, is depleted (55). Consequently, excess acetaminophen is mainly metabolized by the CYP2E1 enzyme in the liver, and with no further glutathione available, N-acetyl-P-benzo-quinone-imine (NAPQI), a substance with remarkable liver toxicity is produced, resulting in the destruction of liver tissue and ultimately liver failure (55).

NAC functions by providing precursors of glutathione synthesis, resulting in an increased availability of glutathione for the metabolization of acetaminophen to non-hepatotoxic substances (56). NAC application following acetaminophen intoxication has shown a significant reduction of liver damage parameters aspartate aminotransferase (AST) and alanine transaminase (ALT), as well as a reduction in mortality (56).

The initial intravenous dose consists of 150 milligrams per kilogram, applied in 15 minutes, followed by 50 milligrams per kilogram for the next four hours, and 100 milligrams per kilogram over the following 16 hours (57). Recent publications have shown that an application timespan of 12 hours consisting of 100 milligrams per kilogram the first two hours and then 200 milligrams per kilogram for 10 hours reduces adverse emetic events significantly (57).

1.4.5 Atropine

Atropine is an anticholinergic drug utilized to counteract poisonings with substances that function via cholinergic pathways such as organophosphates or chemical warfare gases. In addition, it could also be utilized as symptomatic treatment of non-hypoxia induced bradycardia following poisoning with a plethora of substances.

Organophosphates are utilized in agriculture as pesticides and herbicides, and due to their easy accessibility in some regions can be used for self-harm. Intoxications following contact or ingestion of organophosphates results in an inhibition of the enzyme acetylcholinesterase, resulting in a reduced reuptake of acetylcholine and an accumulation in the synaptic cleft (26). Consequently symptoms described in the previous chapter pertaining to the cholinergic toxidrome occur.

Atropine acts as a competitive muscarine receptor antagonist, results in a displacement of acetylcholine from muscarinic receptors, leading to a reduction in cholinergic action (26). Varying recommended starting dose can be found in literature. Commonly 1-3 milligrams of intravenous atropine is recommended in these intoxications, with titration according to the vital signs and until improvement of the patients symptoms can be observed, oftentimes making repeated and high doses necessary (26).

1.4.6 Methylene and Toluidine Blue

Methylene and toluidine blue are substances that can function as partners in redox reactions and are utilized in intoxications to reverse methemoglobinemia. Hemoglobin is an integral part of the red blood cells and binds oxygen facilitating its transport around the body, allowing for organs and peripheral tissues to be oxygenated. Methemoglobin (Met-Hb) is produced when hemoglobin's Fe^{2+} is oxidized to an Fe^{3+} state (58).

Oxidized iron cannot be utilized to transport oxygen and consequently patients with a significant methemoglobinemia suffer from severe hypoxemic symptoms (58). Substances resulting in methemoglobinemia include "Poppers", a colloquial term for a variety of nitrites, packaged in recreational vials meant to be inhaled. When applied in large amounts or consumed orally and/or intravenously, and consequently absorbed into the bloodstream, nitrites oxidize the iron in hemoglobin resulting in reduced oxygen transport throughout the body (59).

Normal Met-Hb laboratory values are around 0-2%, up to 15% Met-Hb saturation is generally tolerated well and symptoms can be unspecific (60). Levels over 15-20% Met-Hb result in dyspnea, tachycardia, severe central and peripheral cyanosis, and failure to respond to oxygen supplementation (59). Over 50% Met-Hb saturation results in severe dyspnea, metabolic acidosis, arrythmias, coma and Met-Hb levels exceeding 70% lead to severe hypoxic symptoms and even death (60).

To reverse the oxidization of hemoglobin toluidine or methylene blue can be used. These substances cause a reduction of Fe3+ to Fe2+, via the nicotinamide-adenine-dinucleotide-phosphate (NADPH) Met-Hb reductase pathway, therefore enabling oxygen transport and resulting in a stabilization of the patient (59). Recommended dosage of toluidine blue following poppers intoxication are 3 milligrams per kilogram body weight (59).

1.4.7 Other Antidotes

A wide variety of substances can be utilized as antidotes in rare intoxications and would exceed the scope of this diploma thesis. These antidotes include but are not limited to andexanet alfa, digitalis antibodies, hydroxocobalamin, ethanol, fomepizole, and glucose.

2 Material and Methods

2.1 Study Design

The data presented in this diploma thesis consist of a monocentric retrospective data analysis including patients from the medical ICU of the Department of Internal Medicine at the Medical University of Graz, Austria. It includes six full years of documented toxicological ICU patient data from the first of January 2013 to the end of December 2018. Following an application to the local institutional review board (ethics committee of the Medical University of Graz), the retrospective data collection was approved (votum number:31-205 ex 18/19).

2.2 Data Collection

The data was obtained from the electronic medical records and charts of all patients admitted to the ICU of the Department of Internal Medicine from the 01.01.2013 to the 31.12.2018. An automated digital search using German keywords in admission files and notes was used to identify potential toxicological patients.

The screening keywords utilized were: Intoxikation, Intoxikationen, Vergiftung, Vergiftungen, Suizid, Selbstmord, Toxikologie, Toxscreen, Screening, Drogen, Rausch, Alkohol and Gift. Furthermore, the ICD-10 Codes T36 until T65, T96, F10.0 until F19.0, 901, 902, 922, 923, 929, 931, 941, 999 und U99.9 were utilized to further screen possible intoxication cases. The consequent detected results in the patients' medical records were then manually screened for appropriateness regarding inclusion and exclusion criteria.

Inclusion criteria consisted of 18-100 year old patients admitted to the medical intensive care unit in Graz from the 01.01.2013 to the 31.12.2018. An intoxication must be determined causational for the ICU stay. Exclusion criteria consisted of patients under 18 years of age, or patients where the ICU stay could not clearly be verified to be caused by an intoxication. In addition, the collection of the data was done on a case by case basis, meaning that patients with multiple ICU stays, due to multiple independent intoxication events were counted separately. Data was utilized in a pseudonymized format, to conform to data protection laws.

The information collected consisted of general demographic data such as age, sex, length of the ICU stay, if the patient was intubated during the ICU stay or was intubated before arrival by preclinical emergency doctors, the timespan the patient was intubated, and if the patient survived. To identify the causational substance or substances patient files, medical records, protocols of emergency personnel, or information from relatives were considered. Primary or secondary toxin elimination or antagonist use (independent if the application was retrospectively valid) was also documented. Primary detoxification included activated charcoal, gastric lavage, whole bowel irrigation, ipecac syrup, and endoscopic medication retrieval. For secondary detoxification extracorporeal toxin removal, repetitive application of activated charcoal, forced diuresis (defined as >5L of intravenous fluid and application of loop diuretics), urine alkalization, HBO, and HIET were considered. Furthermore, the reason for the intoxication was categorized as suicidal, accidental, recreational, iatrogenic, or if not documented, noted as unclear.

It is important to note, that there is no globally standardized method of grouping or categorizing acute intoxications in literature or patient documentation. In order to allow data manageability, without over-simplifying substance groups, it was decided to separate the groups based on the APACHE IV classification system (Table 1)(1).

Group	Substances
0	Unknown
1	Ethanol
2	Analgesics
3	Antidepressants, Antiepileptics and Antipsychotics
4	Street drugs including opiates, cocaine and amphetamines
5	Sedatives
6	CO, Arsenic and Cyanide
7	Other not categorized substances
8	Combined drug intoxications of two or more substance groups

Table 1: Categorization of intoxications according to substance groups (1)

Furthermore, cases were allotted to the group of combined drug intoxications following the application of two or more substances belonging to different groups (Table 1).

2.3 Statistical Data Analysis

The statistical data was initially collected in an Excel document and the analysis and graphical presentation of the data was executed using the program “Statistical Package for Social Sciences” (SPSS®) version 26 (SPSS Inc, Chicago, Illinois, USA).

A plethora of statistical methods were utilized to enable a concise answer to the research question. Discrete variables were evaluated utilizing frequencies and percentages, whereas continuous variables were evaluated utilizing median and 25^{th} – 75^{th} percentile. To compare statistical differences of the data, the Mann-Whitney-U test and Chi-square test were utilized.

3 Results

The keyword ICU document search resulted in a total of 841 possible intoxication cases, whereas the ICD code search yielded 331 results. All of these patient files (n=1172) were reviewed manually for duplicates and appropriateness according to inclusion and exclusion criteria. Consequently, a total of 227 intoxication cases were confirmed and were utilized for the retrospective data analysis (Figure 1).

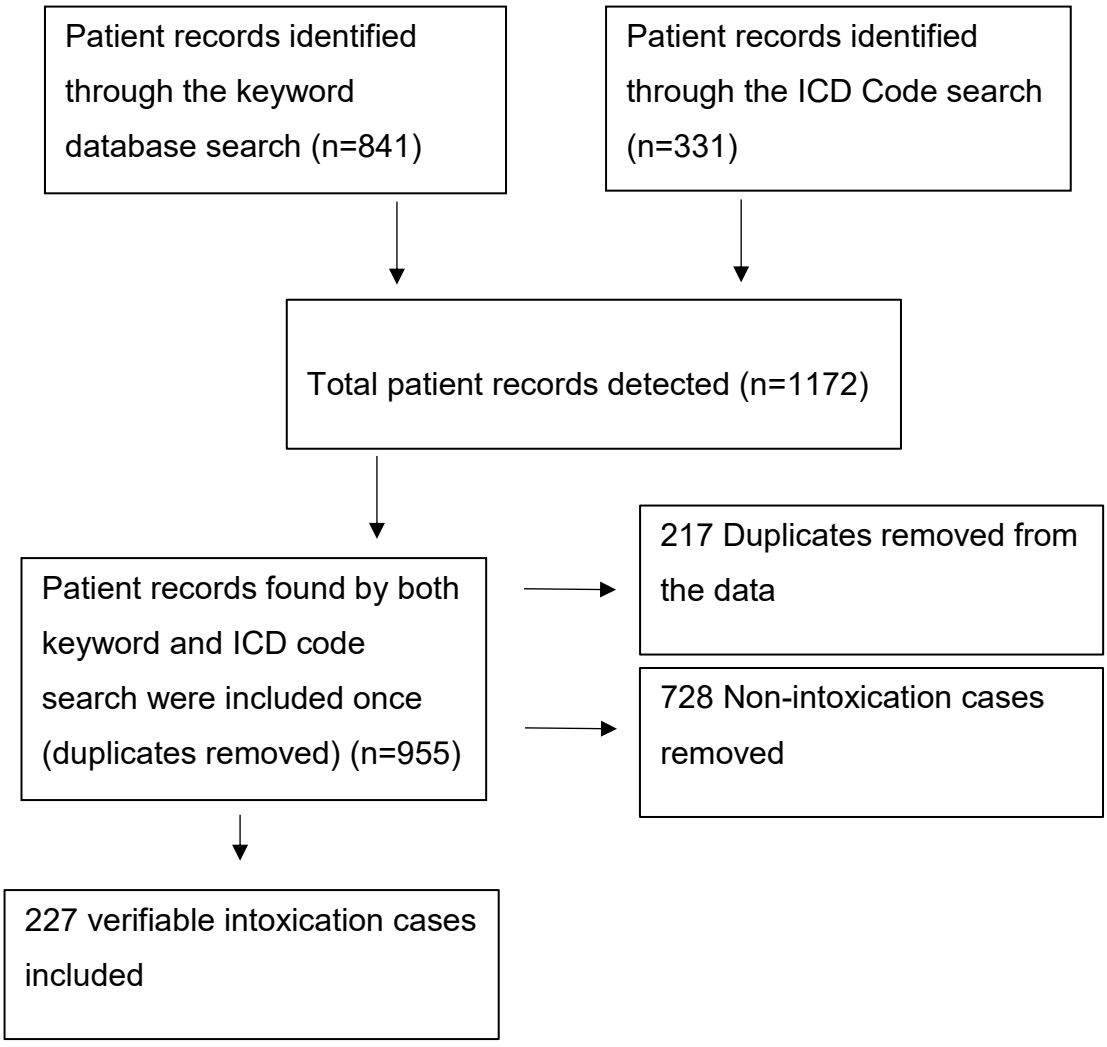

Figure 1: Data collection procedure

3.1 Distribution of Patients per Intoxication Group

In the primary data evaluation, the distribution of patients in the defined intoxication groups were evaluated (Figure 2, Table 2). The most common intoxication was the combined drug intoxication, consisting of 44% (n=100) of all cases.

Following this, Antidepressants, antiepileptics and antipsychotics were shown to be the most common isolated cause for intoxication at 13.2% of all intoxication patients treated in the ICU. Street drug and ethanol intoxications consisted of 10.1% and 9.3% of ICU treated intoxications, respectively. Analgesic substances and sedatives caused around 5% of intoxications each, while isolated CO intoxications were present in 5 patients (2.2%).

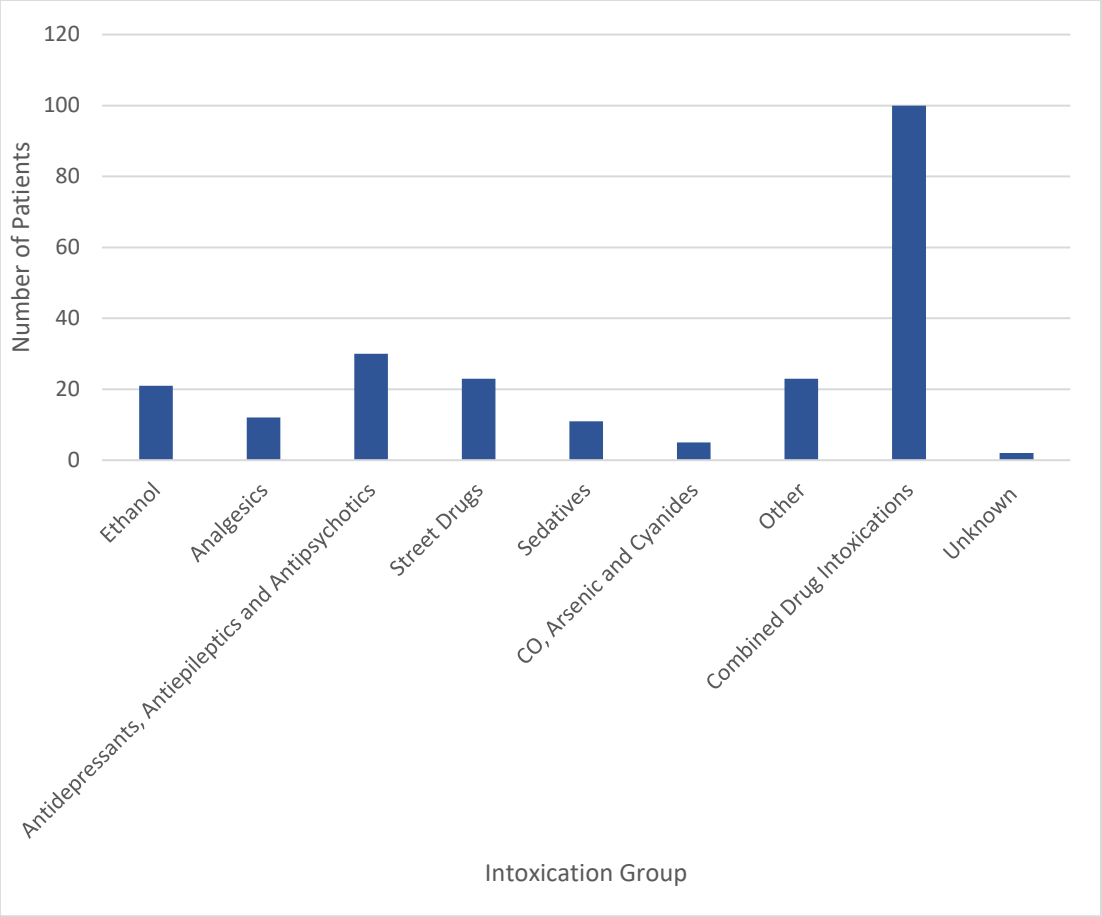

Figure 2: Number of patients per intoxication group

Intoxication	Number of Patients	%
Ethanol	21	9.3
Analgesics	12	5.3
Antidepressants, Antiepileptics and Antipsychotics	30	13.2
Street Drugs	23	10.1
Sedatives	11	4.8
CO, Arsenic and Cyanides	5	2.2
Other	23	10.1
Combined Drug Intoxications	100	44
Unknown	2	0.9
Total	227	100,0

Table 2: Distribution of patients per intoxication group

Of the one hundred combined drug intoxications, 39 patients suffered from an intoxication involving two substances, of which 24 involved ethanol as the second substance. Three substances in combination were the reason for intoxication in 27 patients, of which 6 included alcohol. Four substances were causational in 20 patients, of which fourteen abused alcohol. 5 or more substances were rare, making up for a total of twelve patients. In two further cases it was unclear how many different substances were causational, but had clear indication that a combined drug intoxication was prevalent. In total, half of the combined drug intoxications (n=50/100) included alcohol as an intoxicating substance.

The group “other”, containing a plethora of non-otherwise classifiable substances made up 10.1% of all cases and included the following substances (Table 3).

Substance	Number of Patients
Digitalis	4
Insulin	4
Cleaning and building products	2
Hypertension medications	2
Muscle Relaxants	2
Toxic Mushrooms	2
Water	2
Antihistamine	1
Antivirals	1
Disinfectant	1
Glycerin	1
HCl	1
Total	23

Table 3: Substances categorized in the group other

3.2 Distribution of Intoxication Patients by Sex

In total 124 (54.6%) male and 103 (45.4%) female intoxication patients required ICU treatment. Furthermore, the distribution of different intoxication causes were evaluated according to sex of the patient (Table 4).

Intoxication	Number of Female Patients	Female Patients (%)	Number of Male Patients	Male Patients (%)
Ethanol	6	5.8	15	12.1
Analgesics	8	7.8	4	3.2
Antidepressants, Antiepileptics and Antipsychotics	18	17.5	12	9.7
Street Drugs	4	3.9	19	15.3
Sedatives	8	7.8	3	2.4
CO, Arsenic and Cyanides	1	1	4	3.2
Other	10	9.7	13	10.5
Combined Drug Intoxications	48	46.6	52	41.9
Unknown	0	0	2	1.6
Total	103	100	124	100

Table 4: Number and percentage of intoxication patients per sex and intoxication group

This made evident, that the combined drug intoxication is the most common intoxication among both sexes. In females the second most common intoxication that required ICU treatment was caused by group of antidepressants, antiepileptics, and antipsychotics followed by the group „other“ containing a plethora of non otherwise classifiable substances. Analgesics, sedatives and ethanol make up 5-8% of intoxications in females. Intoxications regarding the groups CO, arsenic and cyanides, as well as street drugs were exceedingly rare.

In males, following the combined drug intoxications, the most common singular substance found in ICU patients requiring treatment were street drugs, resulting in 15.3% of male patients. The third most common substance group in males was made evident to be Ethanol (12.1%), followed by “other” intoxications (10.5%), then antidepressants, antiepileptics and antipsychotics (9.7%). CO, arsenic and cyanide as well as analgesics and sedative intoxications were equally rare each making up for 2-3% of male intoxication patients.

3.3 Distribution of Intoxications Patients by Age Groups

Furthermore, the age distribution of intoxications requiring ICU treatment was evaluated. The median age of intoxicated patients was shown to be 46 years of age, with a 25th to 75th percentile of 29-58 years of age. The patients were grouped into ten year intervals to display the distribution of the number of intoxicated patients per decade (Table 5 and Figure 3).

Age Groups in Years	Number of Patients	%
18-27	46	20.3
28-37	40	17.6
38-47	39	17.2
48-57	42	18.5
58-67	28	12.3
68-77	20	8.8
≥78	12	5.3
Total	227	100.0

Table 5: Number and percentage of intoxication patients per age group

This showed the largest number of patients represented in the 18-27 years of age bracket (20.3%). From age 28- 57 the prevalence of intoxications with necessary ICU admission remained very similar at around 17%. From 58 years onwards the number of ICU admissions due to intoxication events declined.

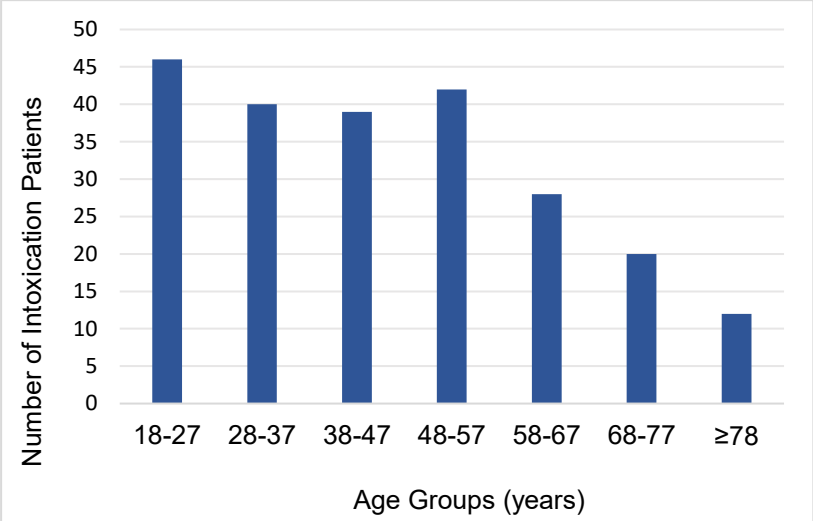

Figure 3: Number of intoxication patients per age group

The distribution of age per sex was also investigated. It was shown that the minimum and maximum age of the patients were 18-86 and 18-91 years in males and females, respectively. The median age of male intoxication patients was determined to be 42 [28-55] years of age and female intoxication patients were median 48 [33-64] years of age and the difference in age was statistically significant (p= 0.019; Figure 4).

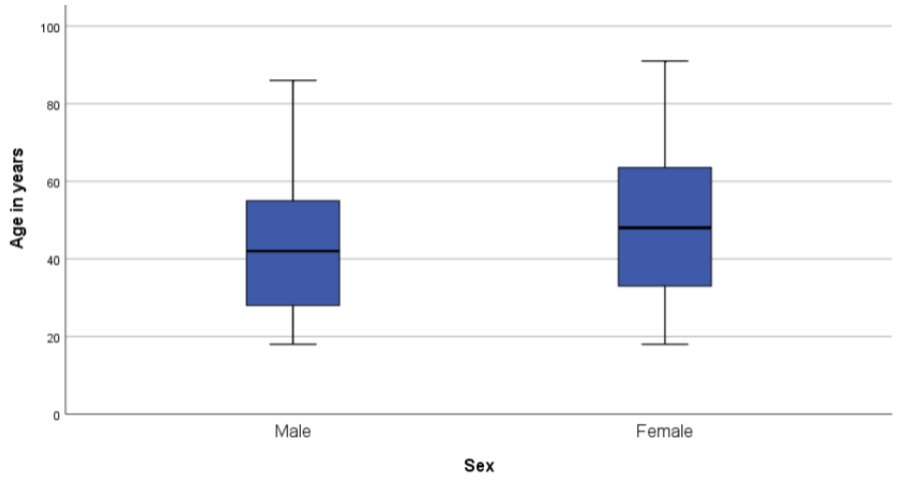

Figure 4: Boxplot of age distribution by sex

3.4 Reason for Intoxication

Furthermore, the reason for the intoxication was evaluated and showed following results (Table 6 and Figure 5). More than half of the patients that required ICU care, stated that the reason for the intoxication was suicidal intent and one quarter of the patients stated recreational usage as the cause. 13.2% were accidental intoxications, and 2.6% iatrogenic in nature. In 7% of patients, no reason could be clearly be identified retrospectively.

	Number of Patients	%
Unclear	16	7
Suicidal	118	52
Recreational	57	25.1
Accidental	30	13.2
Iatrogenic	6	2.6
Total	227	100.0

Table 6: Reason for intoxication

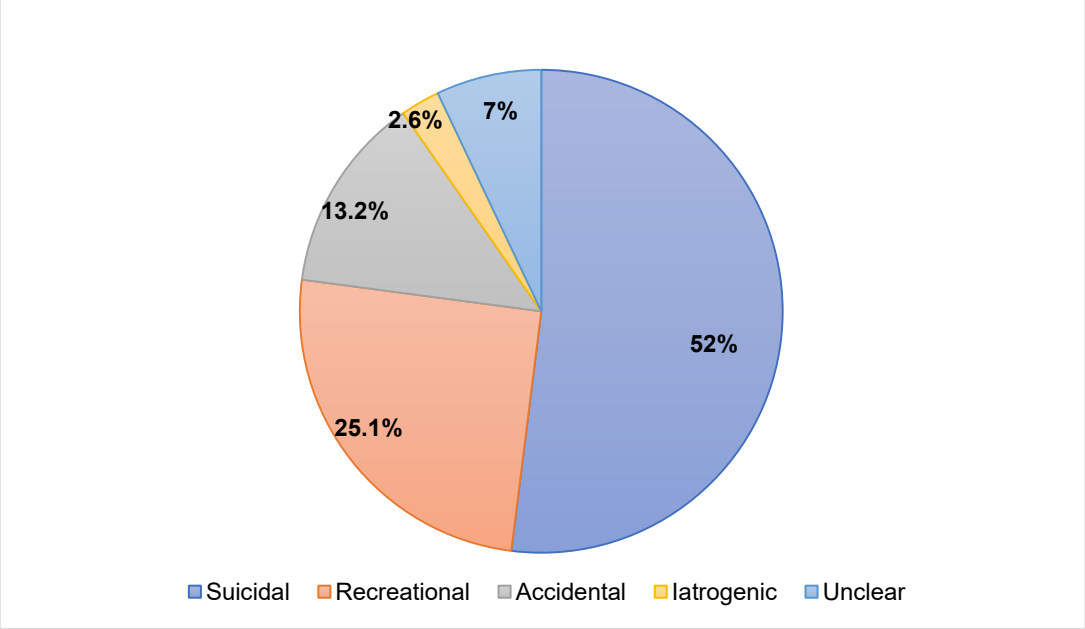

Figure 5: Reason for intoxication

3.5 Intoxication Treatment (Primary and Secondary Detoxification, Antidotes, and Intubation)

Furthermore, key points pertaining to the treatment of intoxications were evaluated, namely if primary or secondary detoxification methods were necessary, if antidotes were given and whether intubation and mechanical ventilation were performed. Some of these interventions were applied preclinically by emergency medicine personnel or in the emergency room and repeated or performed in the ICU.

One quarter of patients (24.7%, n=56) were given activated charcoal as a method of primary detoxification and no other primary detoxification methods were used (Table 7). 15 Patients (6.6%) received secondary detoxification of which 12 received dialysis and three hyperbaric oxygenation. Antidotes were used in 126 cases, of which flumazenil was the most commonly applied substance, followed by naloxone. Examples of other antidotes given in intoxicated patients were acetylcysteine, physostigmine, glucose, biperiden, digitalis antidote, toluidine blue, methylene blue, silymarin, phylloquinone and hydroxocobalamin.

Utilized treatment	Number of Patients	%
Primary Detoxification	56	24.7
Secondary Detoxification	15	6.6
Antidote given	126	55.5

Table 7: Number of patients that received detoxification or antidotes

Females received primary detoxification methods significantly more often than males (33% vs. 18%; p=0.008). In regard to secondary detoxification methods and antidote application, there was no significant difference between females and males (p=0.385 and p=0.263, respectively).

A secured airway and mechanical ventilation was deemed necessary for 38.3 % (n= 87) of patients included in this study. Of these 87 patients, 52 were male (of total 124 males) and 35 female (of total 103 females; Table 8).

Intoxication Group	Female Patients Intubated (Total female Patients)	Male Patients Intubated (Total male Patients)	Total Patients Intubated	Percentage of Patients Intubated per Intoxication Group
Ethanol	0 (6)	10 (15)	10	48%
Analgesics	4 (8)	1 (4)	5	41%
Antidepressants, Antiepileptics and Antipsychotics	5 (18)	4 (12)	9	30%
Street Drugs	3 (4)	7 (19)	10	43%
Sedatives	3 (8)	0 (3)	3	27%
CO, Arsenic and Cyanides	1 (1)	2 (4)	3	60%
Other	2 (10)	3 (13)	5	22%
Combined Drug Intoxications	17 (48)	23 (52)	40	40%
Unknown	0 (0)	2 (2)	2	100%
Total	35	52	87	

Table 8: Number of patients intubated per intoxication group and sex

Considering all 227 intoxication cases in their respective substance groups, 100% of the unknown intoxications were intubated (2/2), followed by a total of 60% (3/5) of all CO cases. Further, a total of 48% (10/21) of all patients with a monointoxication of ethanol were intubated, and all of these patients were of the male sex. 43% of all patients suffering from a street drug intoxication (10/23), 41% (5/12) of patients with an analgesics intoxications and 40% (40/100) of all combined drug intoxications required intubation. Antidepressants, Antiepileptics and Antipsychotics and the group of sedatives required intubation in 30% (9/30) and 27% (3/11) respectively.

When taking into account the comparison of necessary invasive airway management pertaining to the sexes, it was determined that there was no significant difference in the rate of intubation between male and female patients (p=0.220). In addition, the length of intubation was evaluated. Males were intubated a median of 21 hours [11.9-47.1], and females 16.5 hours [7.3-49.5]. There was no significant difference in intubation time for male and female patients (p=0.418).

3.6 ICU Length of Stay

Furthermore, the duration of ICU stay of intoxication patients was investigated. The median stay of patients in the ICU was shown to be 32 hours [18.7- 63] with a range spanning from 1.7 hours of minimum stay to 840.4 hours of maximum stay in the ICU (equating to 35 days).

The median length of stay for male patients in the ICU was 32 hours [19.4-65.2]. Similarly, the median length of stay for females was 32 hours [16.4-63.0]. The length of ICU stay was not statistically significantly different between male and female patients (p=0.443).

3.7 ICU Mortality

In addition, ICU mortality of intoxication patients was evaluated. Nine patients, making up 4% of all intoxication patients requiring intensive care measures, died during their ICU stay. The distribution analysis made evident that three males, and six females passed away in the ICU. Three of the intoxications were combined drug intoxications, and all other groups except for antidepressants, antiepileptics and antipsychotics resulted in the death of one patient. Three of the patients were identified to have had suicidal reasons for the intoxication, three other intoxications were considered accidental, one iatrogenic and in two patients, there was no intention identified.

Of these 9 patients, 5 were resuscitated preclinically and following return of spontaneous circulation transported to the medical ICU for further treatment.
A further two patients were resuscitated during the ICU stay and consequently passed away following termination of cardio-pulmonal resuscitation (CPR). Furthermore, there was no significant difference in ICU mortality between the sexes (p=0.306). Insight into the patients that died in the ICU due to acute intoxications is given in table 9.

Patient	Sex	Age	Intoxication Group	Substance Specification	CPR
1	Male	80	Ethanol	Ethanol	Preclinical
2	Male	51	Other	Insulin Pens	No
3	Male	25	Combined Drug Intoxication	Methadone and Benzodiazepines	Preclinical
4	Female	46	Analgesics	Common cold medication containing 45 g of Paracetamol over 3 months	ICU
5	Female	23	Street Drugs	Urine screening: opioids positive	Preclinical
6	Female	72	Benzodiazepines	Lorazepam and Diazepam	No
7	Female	49	CO	Gas inhalation during house fire	Preclinical
8	Female	35	Combined drug intoxication	Quetiapine, prothipendyl and ethanol	ICU
9	Female	47	Combined drug intoxication	Ethanol and CO inhalation	Preclinical

Table 9: Specification of ICU mortality cases

4 Discussion

Drug and substance abuse, as well as accidental and iatrogenic intoxications requiring real-time constant observation and invasive intensive care treatment have become an integral part of medical intensive care units worldwide. These patients, in the acute phase, oftentimes require airway, breathing and circulatory support, constant monitoring of vital signs, as well as detoxification procedures such as dialysis, which require a high level of care and invasive vascular access requiring specially trained personnel. As a result, it has become imperative to critically evaluate the results of this diploma thesis regarding intoxication patients admitted to the intensive care unit in Graz, and establish a comparison to international data.

We investigated a six year time period and identified 227 patients with intoxications requiring ICU care. Interestingly, for these intensive care procedures including observation and detoxification techniques, patients only required short stays within the ICU. Furthermore, a majority of patients that required invasive mechanical ventilation were intubated for a limited amount of time. A possible reason for the short ICU stays and intubation times could be the half-life of a plethora of medications and drugs being limited to hours. Therefore, patients may be rapidly transferred to step-down units.

The separation of toxicological intensive care patients into nine intoxication groups, was done to establish the first ever collected data displaying the distribution of different intoxication cases in recent years in Graz. Surprisingly, the group of combined drug intoxications were shown to be the most common group, making up almost half of all cases. In an attempt to make the prevalence of substances more clear, the combined drug intoxication group was closely evaluated in reference to the number of substances applied, as well as the role of ethanol in this group. It can be concluded that, as previously suspected, alcohol plays a large role in combined drug intoxications with half including alcohol. Furthermore, the group other enables only limited information as a plethora of varying substances are included and can therefore not easily be utilized in direct comparisons between groups.

Regarding intoxication prevalence by patient age, the largest number of patients were represented in the youngest age bracket of patients 18-27 years of age (20.3%). From age 28- 57 the prevalence of intoxications with necessary ICU admission remains very similar with around 17%. To determine possible causes for the distribution of intoxications at a younger age and to develop mental health and addiction prevention measures, further research and advocacy is necessary. Furthermore, it was made evident that female intoxication patients requiring ICU treatment were statistically significantly older than male patients.

In addition, when investigating the distribution of patients in intoxication groups by sex, an interesting difference in substances causing an ICU stay found. Men were more likely to require treatment following alcohol or street drug use, whereas female patients displayed an increased number of antidepressant, antiepileptics and antipsychotic intoxications, as well as sedative intoxications.

Furthermore, in the evaluation of the diploma thesis data, it became evident that a surprisingly low percentage (24.7%) of patients received activated charcoal as a primary detoxification measure. A possible reason for this, is that oftentimes activated charcoal is considered useful in the first hour following ingestion and adequate protective reflexes such as swallowing and the absence of severe vomiting are necessary for its application. Consequently, the possibility of activated charcoal administration is limited in patients with reduced awareness and alertness. Application therefore requires a concise benefit to risk evaluation.

Possible improvements to patient treatment, could be to further enable and encourage adequate early preclinical administration of activated charcoal. Further research pertaining to the benefits of activated charcoal in intoxications with significant enterohepatic circulation or delayed gastric passage is necessary, as these groups may benefit significantly from this method of detoxification. A german publication by Schwacke et al. determined, similar to our data, that 30% of intoxication patients in an ICU received activated charcoal as a primary detoxification technique (62).

Interestingly, in this diploma thesis it was determined that significantly more females received activated charcoal as a method of primary detoxification in comparison to male patients. A multitude of possible reasons must be considered to explain this phenomenon. It is possible that female patients administer more toxicological substances perorally that can be treated with activated charcoal, however, it is also possible that female patients seek medical assistance earlier and the administration of activated charcoal perorally is therefore possible in a larger number of cases.

Furthermore, a large number of intoxication patients requiring intensive care measures regarding ethanol and street drugs (including intravenous drug abuse) were male, which cannot be treated with activated charcoal.

ICU mortality was surprisingly low with only 4% of intoxication patients passing away. When considering ICU mortality, it is vital to mention, that around the clock availability of emergency preclinical physicians in Austria, it is likely that not all intoxication patients requiring CPR and consequent possible intensive care procedures are transported to the ICU in Graz. If during the complex preclinical decision-making process, it is determined by the emergency doctor, that the patients chances of benefiting from further invasive procedures and CPR are minutely small, then a decision can be made to withdraw care at the patients place of residence.

As a result, the data may vary from other paramedic systems, where different CPR termination protocols are in place. Furthermore, gravely ill intoxications patients, that pass away in their home and are determined to have overt clinical signs of irreversible death, are also not included in this retrospective analysis. Therefore, ICU mortality rates cannot be utilized to infer information about general mortality in intoxication cases.

The University Hospital Graz is a central hospital offering a plethora of advanced and specialized fields as well as offering the only HBO center for Styria and parts of Carinthia. Consequently, it is the only possible destination for patients suffering severe CO and smoke intoxications, therefore resulting in the admission and transfer of severely ill patients from other intensive care units. In addition, the University Hospital Graz also has a specialized center for transplant surgery. Both of these factors must be considered when evaluating the ICU mortality of this specific ICU. Furthermore, we found that 7 out of 9 patients who passed away within the ICU had received cardiopulmonary resuscitation due to the severity of the intoxication, which ultimately results in an extremely poor prognosis.

4.1 Comparison with Global Literature

To be able to draw adequate conclusions pertaining to intoxication patients at the medical intensive care unit in the University Hospital Graz, it is of utmost importance to compare the collected data to international literature. The prevalence of common substances utilized in acute intoxications can vary broadly depending on the regions socioeconomic status, availability of drugs and local medication prescription practice and laws, as well as mental health and addiction measures that are put in place. Furthermore, there is no standardized method of intoxication substance categorization, making direct comparisons exceedingly difficult.

The distribution of male to female patients was shown to be similar in a German study conducted in Heidelberg by Schwacke et. al. The data collected in this diploma thesis made evident that male (54.6%) and female intoxication patients (45.4%) are admitted to the ICU in almost the same ratio (62). Furthermore, regarding age distribution, the median age of intoxication in the ICU in Graz was determined to be 46 years of age across both sexes; 48 years in female patients and 42 years in male patients. Schwacke et. al. separated the group into adverse drug reactions which showed a median of 71 years of age, and intentional intoxications resulting in a median age of 39.

Moreover, Aydin et. al. evaluated the frequency that primary and secondary detoxification as well as antidotes were administered in a medical ICU in Turkey. Thirteen percent of the total 83 intoxication patients received primary detoxification with activated charcoal, 11% dialysis as secondary elimination and 58% of patients an antidote (63). Similarly, the data of this diploma thesis indicate that one quarter of all intoxication patients received activated charcoal and more than half (55%) received any form of antidote.

We did not assess for the appropriateness of the antidote application, and only investigated whether any antidote was given or not. This may result in a higher total number of antidotes given, however, the retrospective evaluation of only correct antidotes given would bias the results. The decision for application of antidotes must be performed at the bedside according to clinical assessment of the patients symptoms, often with little additional information available. This intrinsically leads to retrospectively falsely applied medications after the fact, when the intended effect of the antidote does not take place and when later on more test result may be available.

In a study done by Heyerdal et. al. in Oslo, the ICU length of stay was evaluated. It indicates a median ICU stay of one day, with 58% of patients discharged from the ICU after the first 24 hours and only 11% of patients stayed three or more days (4). Similarly, the ICU length of stay determined in this diploma thesis was also short with a median of 32 hours for both sexes.

Heyerdal et. al. also investigated the cause for intoxication. In the study it was found that approximately 35% listed the reason for intoxication to be definite or possible suicide (4). Furthermore, 24% of patients stated that the reason for intoxication was an appeal for help, another 36% of intoxications were determined to be due to recreational drug use and 4% were reported to be accidental (4). The data in this diploma thesis shows a similar trend, with more than half of all intoxication patients referencing suicidal intentions, one quarter of all patients citing recreational drug use as the reason, and 13% of all patients presenting with accidental intoxications.

In regards to ICU mortality, Heyerdal et.al. reported a mortality of 1.1% of all intoxication patients. ICU Mortality at the medical ICU in Graz was determined to be higher, resulting in the death of 4% of all intoxication patients. Considerations must be made that the medical ICU in Graz is the central hospital for Styria and therefore commonly receives the most critically ill patients, oftentimes following protracted CPR and requiring maximal intensive care treatment.

4.2 Limitations of this Study

When considering the patients included in the study, it is initially important to mention, that this data does not reflect all intoxication cases prevalent in Graz. Due to the inclusion of only those patients requiring intensive care measures, a large majority of the presenting cases in the emergency room were not evaluated and included, and therefore cannot be utilized to generalize and extrapolate data pertaining to the general number of intoxications requiring hospital care. In addition, due to multiple close observation possibilities and monitoring floors in the University Hospital Graz outside of the intensive care unit, it is possible that not all patients fulfilling the intensive care criteria of other hospitals, were admitted to the intensive care unit in Graz. The possibility for close monitoring and the level of care that a ward can provide, varies greatly internationally and must be taken into consideration. Nevertheless, to investigate all intoxicated patients from all emergency departments, intermediate- and intensive care units would have been beyond the scope of this thesis.

Furthermore, it is important to acknowledge, that the information pertaining to the cause of the intoxication and reason for intoxication, were collected from multiple sources. Documentation from the preclinical emergency doctors, information from the emergency medical services, the patient themselves, relatives and in some cases reports from police were used. These preclinical resources are oftentimes vital for the diagnosis, treatment and further management of these patients. The data evaluated in this retrospective analysis was then collected from the intensive care physicians documentation.

This makes evident, that multiple level communication is necessary to diagnose and treat toxicological patients. A substantial part of the collected data pertaining to the substances causing the intoxication were based on the subjective reports of patients and emergency personnel. In some cases, there were no recognizable substances or reason that could be determined. However, all available resources were utilized to classify patients accurately.

The ideal method of inclusion of toxicological patients, would be to only utilize substrate or urine analysis, to confirm the intoxication substance. This, however, is not possible in a plethora of intoxications, depending on the time interval until treatment and diagnostics can be performed, the method of application and the laboratory possibilities of detection. Consequently, a clinical diagnosis based on all available information is usually necessary.

In addition, we defined forced diuresis as the application of at least 5l of intravenous fluids in combination with the use of loop diuretics, as there is no clear consensus or definition in literature. This global heterogenous terminology, however, makes it difficult to differentiate or compare the implementation of forced diuresis as a secondary detoxification method with other reports or publications. We investigated the charts of intoxicated patients to identify if any received forced diuresis per our definition; but found no respective cases. Interestingly, we noted that physicians also used the term “forced diuresis” in their documentation heterogeneously

5 Conclusion

In conclusion, it can be said that this diploma thesis was successful in identifying the most common intoxications leading to an admission to the intensive care unit at the University Hospital Graz over a time span of six years. Furthermore, possible causes, distribution of patient traits such as age and sex, treatment and ICU length of stay and mortality were evaluated and can provide valuable information aiding in the decision-making process of treating physicians.

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