Chapter 9
Personalized Anesthesia for GI Tract and Hepatobiliary System

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Patients with end-stage liver disease have a high perioperative morbidity and mortality. The pharmacokinetics and pharmacodynamics of anesthetic drugs are significantly altered in liver diseases. Patients with hepatic diseases have extrahepatic problems like gastrointestinal, respiratory, cardiovascular, coagulopathy, hematological, neurological and renal problems. So, the intravascular volume, and the extra-hepatic effects of liver disease on different organs must be addressed before the surgery. Invasive monitoring is recommended during major surgeries. Close attention should be paid to the liver blood flow, renal function, encephalopathy, and prevention of sepsis (Dabbagh and Rajaei 2013; Farzanegan and Zangi 2017). The dose of thiopental and propofol should be reduced in these patients. Etomidate may be used safely but offers little advantage over thiopental. Chronic alcohol use may increase anesthetic requirements, but all IV agents should be used with great care. The metabolism of succinylcholine may be slowed because of the reduced pseudocholine esterase concentrations, but in practice this causes few problems. There is an apparent resistance to non-depolarizing neuromuscular blockers in patients with liver disease, which may be due to an increased volume of distribution or altered protein binding. Vecuronium and Rocuronium, both steroid-based NMBs, have a prolonged elimination phase in severe liver diseases. Cisatracurium may be the drug of choice but in all cases, it is advisable to monitor the neuromuscular function. It seems that remifentanil is a suitable drug for these patients and is ideally suited to intraoperative use as it is metabolized by tissue and red cell esterases, which unlike plasma esterases, are preserved in patients with severe liver disease (Chen et al. 2017). Regarding volatile anesthetics, isoflurane, sevoflurane, and

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Desflurane undergo minimal hepatic metabolism and can be regarded as safe (Dabbagh and Rajaei 2011; Mahboobi et al. 2012). Desflurane, being the least metabolized and providing the quickest emergence from anesthesia, is probably the ideal volatile agent. Abnormal liver enzyme test results may be seen in up to 4% of normal individuals and up to 36% of psychiatric patients, although the prevalence of clinically significant hepatic dysfunction in these individuals is less than 1%, suggesting that further costly preoperative testing is unnecessary in asymptomatic patients. Patients with asymptomatic elevations in serum transaminase levels (less than two times the normal values) may undergo surgery with minimal impact on perioperative outcome.

Retrospective data suggest that patients with acute hepatitis from any cause are at increased risk for hepatic failure and death after elective surgery. Thus, elective surgery should be delayed in these individuals until the resolution of the acute hepatocellular dysfunction can be confirmed. Asymptomatic patients with any form of chronic hepatitis should be carefully assessed before elective surgeries, and meticulous care should be taken to maintain hepatic perfusion in the perioperative period and to avoid any hepatotoxic drugs or significant hypotension that may result in liver failure or hepatic encephalopathy (Talebi et al. 2017). Diseases of the gastrointestinal system frequently result in abnormal gastric function, with potentially increased anesthetic risk caused by increased intragastric pressure, delayed gastric emptying, gastric dilation, and increased gastric secretion. Although volume, pH, and amount of particulate matter in the aspirate appear to be the three most important factors determining the severity of the pulmonary insult, overall medical fragility of the patient is often the most important determinant influencing the clinical course and outcome of pulmonary aspirations. Extensive bowel, pancreatic, or esophageal resections entail considerable morbidity with potential serious postoperative complications. Laparoscopy entails the installation of gas into the peritoneal cavity with physiologic changes resulting from this gas under pressure and subsequent surgical positioning. Hemodynamic compromise may occur, which, although rare, can be catastrophic. Anesthetic care of these patients is especially challenging. If the lower esophageal sphincter is not functioning properly, or if a hiatal hernia exists, stomach contents may reflux into the esophagus and pharynx during anesthesia and surgery, increasing the potential for serious aspiration pneumonia. During laparoscopy, the development of pneumothorax and/or pneumomediastinum is a serious and/or potentially life-threatening complication. Approximately 40% of the patients with gastroesophageal reflux have delayed gastric emptying, and in approximately one-third of these, the delay is clinically significant. Maneuvers necessary for a blunt esophagectomy are capable of causing serious hemodynamic and ventilatory compromise, and require appropriate monitoring of blood pressure and respiration. Bariatric surgery patients may have significant medical problems and their perioperative care can be quite challenging. Newer procedures continue to lessen both morbidity and mortality (Amornyotin 2013).

Metabolomics

The optimization of drug therapy according to the personal characteristics of patients is a perspective direction in modern medicine. One of the possible ways to achieve such personalization is through the application of "omics" technologies, including the current promising metabolomics methods (Dabbagh and Elyassi 2016; Dabbagh 2020). In the present postgenomics era, the significance of metabolomics as one of the latest "omics" areas for the assessment of drug effectiveness and toxicity has increased significantly. The utility of metabolomics in anesthesiology is not surprising. Genes and genetic risk scores can be used to indicate what might happen in terms of biochemical or cellular functions, whereas metabolic profiling and metabolic phenotyping indicate what is happening at a biochemical level. Metabolic profiling, which can simultaneously identify thousands of metabolites, has shown significant results in many scientific and clinical applications to date.

Pharmacometabolomics is a new approach based on the practical application of metabolite profiles of easily accessible biofluids. This approach can be used to predict the effectiveness of a drug prior to dosing, and to monitor the post-dose effectiveness of the medication and the disease development, thus avoiding ADR. Pharmacometabolomics is a personal approach to the therapy that achieves the goal of personalized medicine: "the right drug for the right patient at the right dose". One of the main problems of implementing Pharmacometabolomics in clinical practice is the difficulty of standardizing the metabolomics methods (Balashova et al. 2018).

The field of metabolomics is expressed as the study of small-molecular-weight molecules involved in the metabolism, with a focus on how their levels change and/or which metabolites are more involved in response to different drugs or pathologies (Chen et al. 2017). Metabolomic profiling can be applied to the spectra obtained in vitro (e.g., urine, blood, or cerebrospinal fluid) using mass spectrometry or nuclear magnetic resonance, or in vivo from the brain, using magnetic resonance spectroscopy (1 HMRS) (Chan et al. 2009). An advantage of metabolomics is its perfect ability to track multiple metabolites concurrently by a noninvasive approach in the live human or animal brain. There are a few studies regarding metabolomics in anesthesia which is a new and rapidly growing field. Makaryus et al in their work compared the metabolic profile during propofol with isoflurane anesthesia, and showed that prolonged isoflurane anesthesia was characterized by higher levels of lactate and glutamate compared to long-lasting propofol. In contrast, propofol anesthesia was characterized by very low concentrations of lactate as well as glucose. They showed that lactate was fivefold higher with isoflurane compared to propofol anesthesia and independent of lactate in blood (Makaryus et al. 2011). This finding is so important for the ones who have hepatobiliary problems or undergo these surgeries especially if they have hypoperfusion. Liu et al in their experiment showed that sevoflurane anesthesia causes significant oxidative stress, neuroapoptosis, and cellular ultrastructure damage which is associated with altered organ metabotype in

the neonatal rat. The metabolism and metabolomics of ketamine remain poorly understood. Results of a recently performed study showed that, based on the time course of their appearance and due to the low levels of ketamine registered, active metabolites are expected to be involved. Most of its effects are due to the binding of ketamine and metabolites such as norketamine and dehydronorketamine to the serum proteins, mainly albumin and a1-acid glycoprotein (Dinis-Oliveira 2017). Ghini and colleagues evaluated metabolomics profiling of pre and post anesthesia plasma samples of colorectal patients obtained via ficoll separation and showed that, samples collected during anesthesia are not suitable for metabolic profiling studies aimed at patient stratifications, because interpersonal variations are reduced by the overall depression of the metabolites' levels. On the other hand, this study showed that the plasma metabolomics might represent a valuable tool to monitor the effects of different sedatives and/or the individual metabolic responses to anesthesia, providing hints for an appropriate tuning of personalized sedation procedures (Ghini et al. 2015). Jiang et al in their study demonstrated that prenatal exposure to sevoflurane disturbs methylation and arginine/proline metabolism, which may impose adverse impacts on neurodevelopment of offspring and contribute to the neurotoxicity on offspring's generation after sevoflurane anesthesia in adult animals during pregnancy (Jiang et al. 2017).

As most of inhaled anesthetics are metabolized in liver, regulating the methylation and the arginine/proline metabolism can be as the potential therapeutic way for preventing inhalational anesthetics from impairing neurodevelopment, being very important for anesthesia during pregnancy. Jacobs with his colleagues evaluated the metabolomic differences between an inhalant and an intravenous anesthetic observed in the rodent brain and showed that isoflurane anesthesia was characterized by higher concentrations of lactate, glutamate, and glucose in comparison with propofol. They also showed a higher glucose and lactate with sevoflurane in the human brain compared to propofol, which could reflect greater neuronal activity with sevoflurane, resulting in enhanced glutamate-neurotransmitter cycling, increased glycolysis, and lactate shuttling from astrocytes to neurons or mitochondrial dysfunction. Further, the association between the emergence delirium and lactate suggests that the anesthesia-induced enhanced cortical activity in the unconscious state may interfere with rapid return to the "coherent" brain connectivity patterns, required for normal cognition upon emergence of anesthesia (Jacob et al. 2012). So in patients with liver dysfunction being at the risk for neurological disorders, like delirium or cognitive dysfunction, after the anesthesia, intravenous anesthetics may be beneficial. Emergence of anesthesia as the ending stage of anesthesia is not simply the reverse process of induction. Recent findings demonstrated that induction and emergence are partly subjected to the control of different neural pathways. Having knowledge of these mechanisms may help prevent a large percentage of anesthesia complications. Consequently, a better understanding of anesthesia emergent neurobiology could open a new era in anesthesiology, aiming to design new and safer anesthetic strategies, which can be a hot topic for metabolomics in the anesthesia practice.

The mammalian gastrointestinal tract has co-developed with a large number of microbes in a symbiotic relationship, having essential roles in health and disease. Since dysbiosis of the gut bacteria results in the alterations in the levels of certain microbial and host co-metabolites, identifying these markers could enhance the early detection of diseases. So, these metabolic fingerprints can give us clues, as to how to manipulate the microbiome to promote health, or treat diseases, and finally better manage the anesthesia and drug therapy to decrease the complications (Daliri et al. 2017).

Proteomics

Genes are the main sites of biologic information, but proteins are the main sites of biologic activity, giving proteins a unique importance. Proteomics is the study of all the proteins encoded by the genome present in specific tissues, cells, or fluids. It is not only the study of differences in protein levels, but also the study of the modifications that occur after the protein synthesis. Study of the proteome is particularly important because the levels of the mRNA often do not correspond to the levels of the protein product. Unfortunately, proteins are much more complex than DNA and RNA, in a variety of ways. Proteins are composed of 20 amino acids rather than the four nucleotides that constitute DNA and RNA. The three-dimensional structure of the proteins, which is critical to their function, usually is much more complicated than the three-dimensional structure of DNA. The complexity of proteins has slowed the development of high-throughput methods for the examination of large numbers of proteins simultaneously. Nevertheless, great progress has been made in this field and a number of new techniques are being developed to enhance the use of proteomics for studying the diseases (Stelzhammer et al. 2011).

Numerous genomic variants with demonstrated clinical utility have been identified, opening the way for their application to help individualize the drug use for optimal outcomes. As a result, the routine integration of these data to anesthesia as the individualized protocol, has the potential to reduce healthcare costs and improve patients' outcomes, safety, and satisfaction.

Futterer and colleagues in their study showed that exposure to Desflurane can alter the levels of protein expression in the organs. These included alterations in the proteins involved in cellular trafficking, mitochondrial function and signal transduction. These changes were shown to be continued until at least 72 h after the anesthesia, which emphasize that the physiological effect of the anesthetics can extend after immediate postoperative period (Fütterer et al. 2004). Proteomics expresses an ideal field for understanding of the patient specific drug responses which is important in the pharmacokinetic properties of anesthetic drugs. For example regarding pain management, physicians should know information about the individual patients' opioid receptor profile, like the density of the receptors and the response of the receptors to analgesics, to manage the best pain control protocol for each person (Birch et al. 2004). Also such information should help guide the dosing of the

neuromuscular blocking agents, which need extensive hepatic metabolism for their clearance. Screenings of the inhaled anesthetics for large pools of both soluble and membrane-associated proteins, and lipids, show important information regarding the identification of the specific sites of action. The use of proteomics can help to optimize perioperative transfusions, thus decreasing the related complications like infections, allergic reactions and transfusion related acute lung injury (Reddy and Perrotta 2004; Talebi et al. 2017).

In the future the preoperative evaluation and the risk stratification will move beyond chest radiographs, electrocardiography, and physical examination. Different samples will likely be evaluated for proteomic analysis and serum enzyme profiles. Finally, the use of proteomics methodology for solving these questions is almost certain to improve the scientific foundations of the discipline and to enhance the patient care.

It is conceivable that, in a not very distant future, the patients undergoing anesthesia will have genetic profiling, drug metabolizing enzymes, carrier proteins, and receptors to detect life-threatening risk factors, as part of their preoperative screening. All these will enable anesthetists to provide personalized care using agents that their pharmacokinetic profile are best suited to those individuals. Hence, in our era of evidence-based practice, clinical studies that attempt to evaluate the "OMICS" area would undoubtedly reinforce the body of evidence conducive to tailoring medicine, and would offer targeted drug choice and dosing based on each individual's genetic profile.

Microbiomics

When metadata on human microbiome are considered, the entire microbiota-host-exposome phenotype can be generated for each patient, including microbiome profiling that complement the phenotype of the disease (metadata or phenomics data). Moving from omics' or big data to fused and small data, the stratification of the patients can be tremendously improved, translating this process into a potential better health care and go toward generation of decision-support systems for optimized diagnostic pipelines and clinical interventions (Dabbagh 2020).

Proposed and possible mechanisms of which the intestinal microbiome influences the host response during GI surgeries are as followings: surgical stress, blood loss, starvation, release/suppression of host compensatory signals (cytokines, opioids, ischemic metabolites), shift in community structure, diversity and phenotype (virulence), bacterial information processing, Iterative loop of intra species, interspecies and interkingdom signal exchange) and pathoadaptive immune response (ileus, leak) (Duneau et al. 2011).

The vast majority of wound infections occur as a result of intraoperative microbial contamination. Ileus is due to excessive and inappropriate handling of the bowel during surgery and the inappropriate use of opioids. When a patient is operated on by a high-volume, well trained, and highly experienced surgeon and

develops an anastomotic leak, it is due to a technical error (ischemia, tension, poor technique) (Ljungqvist et al. 2017).

Results of a recently performed study showed that the gut microbial compositions in post-surgery colorectal cancer patients were significantly different from those in pre-surgery colorectal cancer patients and healthy individuals and had a significantly lower alpha diversity and a looser ecological interaction network. This change in in these patients was significantly associated with lymphatic invasion. We can conclude that microbiota was probably considered to be the valuable biomarkers in evaluating the condition of post-surgery colorectal cancer patients and recovering the intestinal health (Drago 2019). Mucus microbiome of anastomosis tissue during surgery has a predictive value for colorectal anastomose leakage. Patients seem to have a higher risk of developing anastomosis leakage when their microbial diversity is low, which in turn is often associated with an overabundance of members from the mucin degrading families Lachnospiraceae and Bacteroidaceae (van Praagh et al. 2019). Using fecal microbiota transplantation can decrease the surgical induced dysbiosis and use as a targeted strategy in personalized anesthesia in perioperative period for decreasing post op complications (Wang et al. 2019). Schmitt et al showed the same results for decreasing postoperative complications after pancreatic surgeries (Schmitt et al. 2019). For making surgery safer and further reduce complications, a molecular, genetic and functional understanding of the response of the gastrointestinal tract to alterations in its microbiota is needed. Methods can then be developed to preserve the health-promoting functions of the microbiota while at the same time suppressing their harmful effects.

Personalized Medicine in Bariatric Surgeries

Bariatric surgery has increased dramatically in the past two decades due to data demonstrating decreased long-term mortality and disease burden and cost-efficacy (Butler and O'Rourke 2013). From a practical view, however, adequate resources in the form of health care dollars and surgeons simply do not exist to offer surgery to all candidates. Patient selection is therefore of critical importance. The results of Zechner et al. study showed that MC4R can be used as a predictor of diabetes remission. So this marker can be used as a screening test for selection of patients who are candidate for bariatric surgery and have concurrent diabetes mellitus (Zechner et al. 2013).

On the other hand, surgical management of obesity requires understanding the genetic and epigenetic factors that play a crucial key role in obesity development and weight loss response. Given the concepts of nutritional genomics, defining a "nutrigenomic risk score" or a "nutrigenomic profile" for each individual may represent a novel therapeutic approach for the management of obese patients submitted to bariatric surgery as a targeted therapy for personalized anesthesia (Nicoletti et al. 2017).

There is strong academic and public interest in advancing personalized medicine, which promises more precise, efficient patient care. The infrastructure of a successful personalized anesthesia should have four essential components (Iravani et al. 2017; Sezari and Dabbagh 2019):

1. Genomic/molecular data acquisition,
2. Integration of genomic diagnostic testing and targeted imaging,
3. Research focused on functional genomic targets, and
4. Development and informed use of targeted therapies/drugs of actionable genes

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