orphanaesthesia

Anaesthesia recommendations for

Gitelman syndrome

Disease name: Gitelman syndrome

ICD 10: E26.8 Other hyperaldosteronism

Synonyms: Hereditary hypokalaemia-hypomagnesemia syndrome; Primary renal tubular hypokalemic hypomagnesemia with hypocalciuria

Disease summary: Gitelman syndrome is a recessively inherited condition that reduces the function of the thiazide-sensitive sodium-chloride cotransporter (NCC) in the distal convoluted tubule of the nephron. With an estimated prevalence of approximately 1 to 10 per 40,000, Gitelman syndrome is the most frequently known inherited tubulopathy [1]. Laboratory evaluation typically shows hypokalaemic hypochloraemic metabolic alkalosis with hypomagnesaemia and decreased urinary excretion of calcium (hypocalciuria) with otherwise normal kidney function, analogous to the pharmacological effects of thiazide diuretics. Patients most commonly have low-to-normal blood pressure due to plasma volume contraction (despite high renin and angiotensin levels) and salt craving. Thirst and polyuria, muscle cramps, fatigue and generalized muscle weakness have also been reported. Tetany may occur occasionally, likely related to hypomagnesaemia (<20%) [1]. Chondrocalcinosis can occur later in life.

The most dangerous complication is the development of a long QT syndrome leading to severe arrythmias (e.g., torsade de pointes, ventricular fibrillation) or hypovolaemic shock due to excessive salt loss. Anaesthetic management is defined by the electrolyte disturbances and their symptoms. Therefore, preoperative assessment must focus on the electrolyte alterations and, if deemed necessary, correction should be performed, bearing in mind that these patients are typically used to their altered electrolyte profile and that any correction is of a very transient nature due to the large urinary losses, which are further exacerbated by supplementation. For this reason, plasma levels are highly dependent on the timing after the last supplementation. A steady infusion during and around the procedure is likely the safest option for stabilization of electrolyte abnormalities. Patients must be monitored with an electrocardiogram to identify arrhythmias and repolarization abnormalities. This monitoring must be continued throughout the perioperative period and always in case of electrolyte disturbances. Medications prolonging the QTc-interval and those causing hypokalaemia or hypomagnesemia should be avoided. The anaesthetist should be aware of unexpected episodes of severe hypotension. Physiological considerations indicate that patients might not respond adequately to vasopressors; however, real-life data is still lacking.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Emergency information

A	**AIRWAY / ANAESTHETIC TECHNIQUE**	Gitelman syndrome is not typically associated with the presence of a difficult airway.
B	**BLOOD PRODUCTS (COAGULATION)**	No special preparation / storage of blood products is necessary in patients with Gitelman syndrome. It is not associated with coagulatory disorders.
C	**CIRCULATION**	Prior to surgery, a 12-lead ECG should be provided. Long QT syndrome might be present and severe arrhythmias might be caused by hypokalaemia and hypomagnesemia. Unexpected episodes of severe hypotension must be expected. Vasopressor therapy might be less effective than expected.
D	**DRUGS**	Medications causing hypokalaemia or hypomagnesemia should be avoided. Also, drugs prolonging the QTc-interval must be avoided.
E	**EQUIPMENT**	Standard monitoring should be administered throughout the complete anaesthetic period. A defibrillator should be close by.

Typical surgery

Patients may require anaesthesia for any reason.

Type of anaesthesia

At present time, a definite recommendation can neither be given for general nor for regional anaesthesia.

Necessary additional pre-operative testing (beside standard care)

Due to the variety in their symptoms and the degree of electrolyte imbalances, patients with Gitelman syndrome should be assessed carefully prior to anaesthesia. Specifically, the medical history should clarify if electrolyte supplementation (e.g. magnesium or potassium) has been prescribed [2]. Obtaining a history of the frequency and severity of tetany and muscle weakness serves as a good indicator of disease severity. Reviewing the patient's current medications is crucial to identify any drugs prolonging the QTc-interval or affecting the electrolyte homeostasis. Typically, the following tests should be performed:

- Measurement of electrolyte levels, particularly potassium, magnesium, and calcium levels are essential.
- Patients with Gitelman syndrome might develop chronic kidney disease due to either chronic hypokalaemia or chronic volume depletion and increased renin-aldosterone levels [1]. Kidney function should be assessed through tests (serum creatinine, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR)).
- Given the potential for electrolyte imbalances to affect cardiac function, a 12-lead-ECG must be performed prior to anaesthesia to assess rhythm, heart rate, and QTc.
- Pre-operative measurement of blood pressure must be performed to identify hypotensive patients. If available, information of 24-hours-blood pressure measurements are valuable.

Particular preparation for airway management

Not reported.

Particular preparation for transfusion or administration of blood products

Not reported. It seems reasonable to correct immediately hypokalaemia or hypercalcaemia following repeated transfusion of fresh frozen plasma or platelet concentrates containing citrate, as they may trigger arrhythmias.

Particular preparation for anticoagulation

Not reported.

Particular precautions for positioning, transportation and mobilisation

Sudden changes in patient position should be avoided due to increased vulnerability to hypotension.

Interactions of chronic disease and anaesthesia medications

QT-prolonging drugs should be avoided (for more information see for example https://www.uptodate.com/contents/image?imageKey=CARD%2F57431) [3–5]. Careful monitoring of QTc should be performed, taking age-related changes into account. In addition, drugs associated with hypokalaemia and hypomagnesaemia should be avoided or used with caution in patients with Gitelman syndrome (for a detailed list of medication, see Blanchard et al. [1]).

Anaesthetic procedure

The following recommendations regarding the anaesthetic management of patients with Gitelman syndrome are based on physiological considerations and case reports [2–4, 6–9].

Fasting times should follow regular anaesthetic guidelines.

Hypokalaemia and hypomagnesaemia can potentiate the effects of local and general anaesthetic agents, such as during neuromuscular blockade during general anaesthesia and adrenalin use in regional blockade. Therefore, electrolyte imbalances should be identified and treated as early as possible. For this purpose, high supplement dosages may be necessary. It must be noticed that achieving normal values may not be possible due to ongoing urinary losses. Therefore, the patient´s individual range should be determined prior to anaesthesia, with at least aiming for a range close to normal. There is no definitive evidence to suggest exact preoperative levels of potassium and magnesium that are safe. In the general population, the UK National Institute for Health and Care Excellence (NICE) guidelines suggest aiming for potassium levels of above 3.0 mmol/l and magnesium above 0.5 mmol/l [10]. If hypomagnesaemia is ≤0.5 mmol/l, potassium should be kept ≥3.3 mmol/l. It must be noticed that hypokalaemia, hypomagnesemia, and baseline QTc prolongation are prominent risk factors for drug-induced torsade de pointes and must therefore be avoided. This is particularly important for patients with conditions leading to hypokalaemia, such as chronic vomiting, diarrhoea, and preoperative bowel preparations. Beta-2 agonists and insulin may also cause hypokalaemia because of the intracellular shift of potassium.

There is no evidence for the superiority of a specific type of anaesthesia. The choice of medication should base on its influence on electrolyte homeostasis and the QTc interval. For instance, Droperidol, 5-HT3 serotonin-receptor antagonists, and amiodarone are known to prolong the QT interval and should therefore be avoided. Safe application of sevoflurane is reported; however, it is also known to prolong the QTc-interval. Additionally, hypercarbia, hypoxia and hypothermia must be avoided, as they may increase sympathetic tone resulting in QTc-interval prolongation.

Although Gitelman syndrome does not directly affect drug elimination, severe impairment of kidney function may affect the clearance of certain drugs (e.g., opioids and muscle relaxants).

Patients with Gitelman syndrome are at risk for hypotension due to plasma volume contraction. While the underlying mechanisms are not fully understood, can be seen in these patients. Even though data supporting clinical relevance is lacking, physiological considerations regarding vascular tone in patients with Gitelman syndrome might indicate a decreased response to vasopressors [11]. Therefore, propofol should be used with care, even though successful application had been described in case reports. One potential strategy to address perioperative hypotension is to prioritize intravenous fluid administration in fluid-responsive patients and correct electrolyte abnormalities rather than resorting to vasopressor agents. Anaesthetic management should aim to achieve a balanced intravascular volume status.

Succinylcholine should be used with particular caution due to its potassium-releasing effects (particularly if potassium has priorly administered). If general anaesthesia with muscle relaxants is being considered, the use of a peripheral nerve stimulator is mandatory. Preferably, cis-atracurium should be used for muscle relaxation.

Pain, agitation, and postoperative nausea and vomiting (PONV) may increase the risk of torsade de pointes; therefore, their prevention is critical. Consequently, a liberal approach to the prophylaxis of PONV should be considered, and adequate pain management for the postoperative period must be provided. Furthermore, these conditions can lead to hyperventilation, resulting in an exacerbation of respiratory alkalosis, which may acutely worsen hypokalaemia.

Particular or additional monitoring

Provisions for electrolyte monitoring should be established. Patients should be monitored at least with ECG, blood pressure monitoring, and plethysmography until the discharge from the PACU. The need for advanced hemodynamic monitoring depends on co-existing diseases and the extent of surgery.

Possible complications

Patients are at risk for severe hypokalaemia and hypomagnesemia leading to malignant arrhythmias (e.g., torsade de pointes). Providing more detailed protocols for handling emergency situations such as severe arrhythmias or profound hypotension in the context of Gitelman syndrome could improve preparedness.

Post-operative care

Emphasizing the importance of interdisciplinary collaboration in the preoperative, perioperative, and postoperative phases can be beneficial. This might include coordinating care with nephrologists, cardiologists, and primary care physicians to ensure comprehensive management of Gitelman syndrome. Patients with stable electrolyte status and no need for intensive care treatment for other reasons may be managed in the PACU. Postoperative care should aggressively address anxiety, pain, agitation, and postoperative nausea and vomiting to prevent hyperventilation and subsequent reactive hypokalaemia. Prior to the transfer to the normal ward, a blood gas analysis should confirm a stable electrolyte status. In cases with unstable electrolyte conditions, patients should be monitored in the intensive care or intermediate unit.

Hypokalaemia might lead to an increased risk for paralytic ileus, which is particularly relevant for abdominal surgery.

Disease-related acute problems and effect on anaesthesia and recovery

Typical problems include electrolyte disturbances and arrythmias.

Ambulatory anaesthesia

Due to insufficient evidence, no specific recommendation for or against ambulatory anaesthesia can be made. Ambulatory anaesthesia should be performed only in patients with a stable electrolyte condition undergoing minor surgery.

Obstetrical anaesthesia

There are no limitations regarding neuroaxial techniques or general anaesthesia used in obstetrical anaesthesia [8, 12, 13]. However, it should be noticed that the expansion of extracellular volume in pregnancy typically exacerbates the volume and electrolyte problems of Gitelman syndsrome. The stress of labour can lead to hyperventilation and reactive hypokalaemia. All reported anaesthetic techniques may lead to severe hypotension, of which the anaesthetist should be aware.

Oxytocin might prolong the QTc interval and leads commonly to free water retention and hyponatremia. Further, it might aggravate perioperative hypotension. Therefore, it should only be used under stable electrolyte status and normal QTc interval to prevent uterine atony. However, safe single administration of oxytocin after delivery have been reported. Misoprostol might also offer a safe alternative.

References

1. Blanchard A, Bockenhauer D, Bolignano D, et al (2017) Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 91:24–33. https://doi.org/10.1016/j.kint.2016.09.046
2. Urwin S, Willows J, Sayer JA (2020) The challenges of diagnosis and management of Gitelman syndrome. Clin Endocrinol (Oxf) 92:3–10. https://doi.org/10.1111/cen.14104
3. Graziani G, Fedeli C, Moroni L, et al (2010) Gitelman syndrome: pathophysiological and clinical aspects. QJM 103:741–8. https://doi.org/10.1093/qjmed/hcq123
4. Farmer JD, Vasdev GM, Martin DP (2012) Perioperative considerations in patients with Gitelman syndrome: a case series. J Clin Anesth 24:14–8. https://doi.org/10.1016/j.jclinane.2011.04.009
5. Bettinelli A, Tosetto C, Colussi G, Tommasini G, Edefonti A BM (2002) Electrocardiogram with prolonged QT interval in Gitelman disease. Kidney Int 62:580–4
6. Knoers NV a M, Levtchenko EN (2008) Gitelman syndrome. Orphanet J Rare Dis 3:22. https://doi.org/10.1186/1750-1172-3-22
7. Ferreira S, Antunes C, Pereira M, Rodrigues S (2021) Anesthetic management of child with Gitelman Syndrome: case report. Brazilian J Anesthesiol (English Ed 71:588–590. https://doi.org/10.1016/j.bjane.2021.05.003
8. Smith KA, Reynolds ML, Chang EH, et al (2022) Anesthetic Considerations for Cesarean Delivery in a Parturient With Severe Gitelman Syndrome. Cureus 14:10–14. https://doi.org/10.7759/cureus.26260
9. Schneck E, Schaumberg S, Koch C, et al (2013) Anästhesiologisches Management des Gitelman-Syndroms. Anaesthesist 62:728–733. https://doi.org/10.1007/s00101-013-2218-2
10. Gallagher H, Soar J, Tomson C (2016) New guideline for perioperative management of people with inherited salt-wasting alkaloses. Br J Anaesth 116:746–749. https://doi.org/10.1093/bja/aew102
11. Calò L a (2006) Vascular tone control in humans: insights from studies in Bartter's/Gitelman's syndromes. Kidney Int 69:963–6. https://doi.org/10.1038/sj.ki.5000253
12. Calò LA, Caielli P (2012) Gitelman's syndrome and pregnancy: new potential pathophysiological influencing factors, therapeutic approach and materno-fetal outcome. J Matern Fetal Neonatal Med 25:1511–3. https://doi.org/10.3109/14767058.2011.629254
13. Zhang J, Liu F, Tu J (2022) Gitelman syndrome in pregnancy: a case series. J Matern Fetal Neonatal Med 35:826–831. https://doi.org/10.1080/14767058.2020.1803260

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