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ANAESTHETIC AND CRITICAL CARE DILEMMA

Management of SGLT-2 Inhibitors in the Perioperative Period: Withhold or Continue?

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Abstract

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are commonly prescribed in diabetes mellitus and increasingly for cardiorenal protection. They carry the risk of euglycaemic diabetic ketoacidosis (eDKA). Guidelines around the perioperative handling of these medications are limited and some evidence suggests that withholding them can lead to more surgical complications and poorer glycaemic control. This article gives an overview of arguments for and against withholding SGLT-2 inhibitors in the perioperative period.

Key words: SGLT-2 inhibitors; euglycaemic diabetic ketoacidosis; perioperative period

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Introduction

Sodium-glucose cotransporter 2 inhibitors (-gliflozins) (SGLT-2is) are used in the treatment of type 2 diabetes mellitus (T2DM) and provide cardiorenal protection (Androutsakos et al, 2022; Ruste et al, 2024). Emerging evidence suggests that they may also be beneficial in other conditions, such as non-alcoholic fatty liver disease (Androutsakos et al, 2022).

One important risk associated with SGLT-2is is euglycaemic diabetic ketoacidosis (eDKA), this is particularly relevant in the perioperative period (Chow et al, 2023). In elective surgeries, the risk is approximately 0.2% but increases to 1.1% in emergency surgeries (Chow et al, 2023). This complication is difficult to recognise and although there are no easily available figures for morbidity/mortality, it can lead to organ failure and intensive care unit (ICU) admission (Chow et al, 2023).

SLGT-2is prevents the reabsorption of glucose within the proximal convoluted tubule whilst simultaneously causing increased ketone reabsorption. When combined with increased ketone production, caused by fasting or physiological stress, eDKA can occur (Chow et al, 2023).

Guidelines exist for the perioperative handling of these drugs, but they vary in terms of the recommended duration of omission, ranging from continuation to 24 hours, and up to 3–4 days (Handelsman et al, 2016; Chow et al, 2023; Centre for Perioperative Care, 2021). They are based on limited data and focus on distinct patient groups (diabetes mellitus and heart failure). In practice, there is significant overlap

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Table 1. Table summarising case for and against withholding SGLT-2is.

Withhold SGLT-2is	Continue SGLT-2is
Increased risk of eDKA	Poorer blood glucose control. Increased post-operative complications. Increased risk of cardiovascular adverse events. Increased risk of readmission.

SGLT-2is, Sodium-glucose cotransporter 2 inhibitors (-gliflozins); eDKA, euglycaemic diabetic ketoacidosis.

(Centre for Perioperative Care, 2021; Seki et al, 2023). Balancing the perioperative risks of eDKA against poorer glucose control is perhaps more complicated than initially perceived, here this conundrum will be explored further (Table 1).

The Case for Withholding SGLT-2is in the Perioperative Period

The rationale for holding SGLT-2is is primarily due to the risk of eDKA. Whilst the risk is low generally, the perioperative period adds in several risk factors that predispose patients to eDKA (Ge et al, 2021). Periods of fasting, physiological stress (including operations and sepsis), dehydration, gastroparesis, vomiting and trauma all increase the risk of eDKA (Chow et al, 2023). eDKA can have significant impacts on patients' physiology, potentially leading to significant organ dysfunction and failure (Ge et al, 2021). It has been suggested that in all patients having SGLT-2is withheld (regardless of diabetes status), acidosis can occur and there is an increase in plasma ketones (Ruste et al, 2024). Therefore, serious side effects need to be considered, even if the absolute risk is low.

Diagnosing eDKA is clinically challenging. Blood glucose is normal, urinary ketones are often normal despite raised plasma levels and there are likely to be several other differential diagnoses (Chow et al, 2023; Ge et al, 2021). The diagnosis can be delayed or missed, increasing the severity of the patient's condition. Exacerbating this problem is the fact that eDKA can occur days up to (rarely) weeks following the operation, particularly in bariatric surgery (Chow et al, 2023). This delayed onset may well be a result of the reduced and prolonged reduction in caloric intake immediately after surgery, even after SGLT-2is have been restarted as per guidelines.

The risk of eDKA in the perioperative period is thought to be reduced by withholding SGLT-2is (Centre for Perioperative Care, 2021). This forms the basis for current guidelines in diabetics however it should be noted that the timing can be variable, ranging from 3 days to one day (Centre for Perioperative Care, 2021; Seki et al, 2023). They should only be restarted once patients are eating and drinking normally to reduce the risk of developing eDKA (Centre for Perioperative Care, 2021; Seki et al, 2023). The timing of restarting the medication can be difficult to decide on in the context of bariatric or diet-altering surgeries (Seki et al, 2023).

The Case to Continue SGLT-2is in the Perioperative Period

When SGLT-2is is prescribed for anything other than T2DM, particularly cardiorenal protection, The Centre for Perioperative Care guidelines suggest continuation over the perioperative period (Centre for Perioperative Care, 2021). There is a large crossover between the diabetic and non-diabetic populations prescribed SGLT-2is with up to 40% of heart failure patients having T2DM concurrently (Ge et al, 2021). There is an increase in the risk of serious cardiovascular adverse events in the perioperative period. This is also the case when withholding SGLT-2is, therefore, there is a rationale for continuing them even in those with concurrent T2DM (Ge et al, 2021). A retrospective, single-centre study conducted over 4 years with a limited data set of 64 patients showed a risk of eDKA even when SGLT-2is were held perioperatively as guidelines suggested (Ge et al, 2021). This study also found that there was an increase in post-operative complications, readmission to hospital and reduced blood glucose control (Ge et al, 2021).

Discontinuing SGLT-2is results in greater medication changes for patients which may increase instances of drug errors. Moreover, the risk of eDKA can be minimised by patient and staff education, reducing risk factors such as prolonged fasting and dehydration, and ensuring adequate caloric input (Chow et al, 2023).

Conclusion

Guidelines exist for well-delineated patient populations, but they are not always consistent. There is limited data on balancing the perioperative risks associated with withholding or continuing SGLT-2is and do not cover mixed patient cohorts. Although withholding SGLT-2is reduces the risk of eDKA, it may increase post-operative complications and result in poorer blood glucose control. More evidence is required to better understand the perioperative and surgical implications of SGLT-2i management.

There must be a personalised and nuanced approach but regardless of choice, there are significant risks that need to be minimised through vigilance, care and education. Risk factors should be identified early, and a balanced decision must be made. In many cases, there may not be a clear answer, and expert advice should be sought. Practice and guidelines may well change as more evidence is collected regarding SGLT-2is in the perioperative period.

Availability of Data and Materials

All data included in this study are available upon request by contact with the corresponding author.

Author Contributions

ZP was the sole author and was responsible for the design of the work, drafting and revision of content, and approval of the version to be published. ZP has

participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

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