Zaponex Fact Sheet
Clozapine during surgery and anaesthesia

Important Information

The information provided in this fact sheet is intended for healthcare professionals and should not be used as a patient information leaflet.

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on information from scientific literature and previous successful experience. Each case should, of course, be considered individually.

Background

The Zaponex Summary of Product Characteristics (SPC)[1] does not provide any special warnings or precautions for use during surgery. However, in section 4.5 'Interaction with other medicinal products and other forms of interaction', the SPC[1] states;

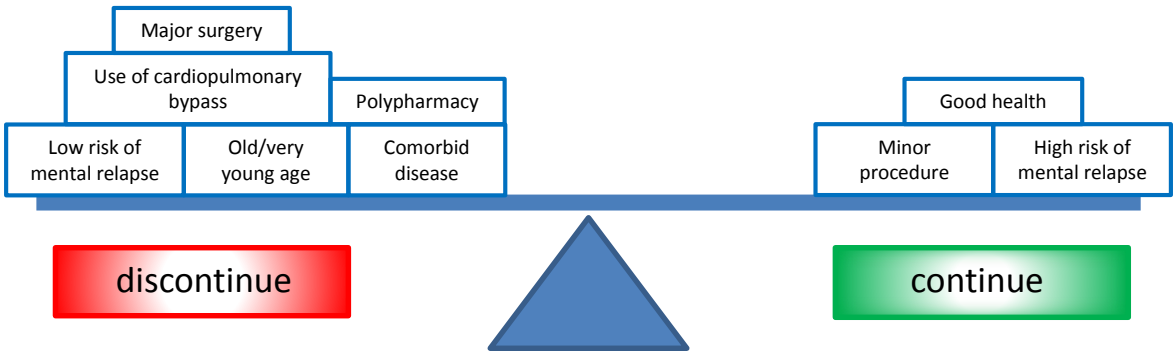
> "Because of the possibility of additive effects, caution is essential in the concomitant administration of substances possessing anticholinergic, hypotensive, or respiratory depressant effects".

Literature only provides a handful of publications on the effects of anti-psychotic drugs during surgery and the anaesthetic process, and these are mostly case reports or retrospective studies. Therefore, there is too little scientific back-up for an evidence-based guideline. Any advice given on this subject is therefore somewhat speculative. This factsheet provides information found in literature complemented with theoretical considerations from the Zaponex medical team.

Factors involved in the decision regarding continuation of clozapine therapy

The main risks posed by the continuation of clozapine during surgery, which could interfere with the effects of anaesthetic drugs, are central nervous system (CNS) depression (*e.g.* sedation), respiratory depression and hypotension. These effects could either be caused or enhanced by clozapine. In addition, both clozapine and certain anaesthetics may lower the threshold for seizures. These pharmacodynamic interactions are discussed in more detail further below.

Figure 1. *Factors that may be taken into account when deciding to stop or continue clozapine.*



For each individual patient the risks of continuing clozapine during surgery should be weighed against the risks of stopping, preferably well in advance of the operation. This should be a decision in which the anaesthetist is closely involved. Various interacting factors should be taken into account (Figure 1). The general health of the patient is, of course, an important issue to consider, as is the age of the patient. Very young or very old age patients may be at increased risk of side effects. Co-morbid diseases and polypharmacy may also form a threat. A large operation may pose a higher risk as it may lead to more profound physiological changes.[2] The use of cardiopulmonary bypass is clearly also a major risk,[3] as it requires close maintenance of the blood pressure.

Obviously, there are also substantial risks involved in withholding clozapine, mostly in terms of mental condition: If the patient is at high risk of mental relapse, this may be a good reason to sustain clozapine continuation.

Kudoh *et al*.[4] studied the effects of discontinuation of antipsychotics before surgery on perioperative outcome in chronic schizophrenic patients. Postoperative confusion in chronic schizophrenic patients who discontinued antipsychotics 72 hours before surgery was significantly more frequent than in patients who continued antipsychotics (31% versus 14%). The frequency of hypotension and arrhythmias during anaesthesia did not significantly differ between chronic schizophrenic patients who preoperatively discontinued and those who continued antipsychotics (16% versus 18%). Therefore, the authors suggested that patients with chronic schizophrenia should continue their antipsychotics preoperatively.[4]

Treatment options and consequences

Of course, uninterrupted continuation and fully stopping clozapine are not the only options; temporarily lowering the dose or omitting a dose, etc. are also strategies that could be considered to allow clozapine use during surgery in order to reduce certain risks, while additionally preventing mental relapse. Due to the sedative and hypotensive effects of clozapine, it is probably sensible to avoid giving a dose of clozapine within 12 hours prior to the operation.

After surgery, the patient needs to be assessed based on their vulnerability to clozapine's side effects (blood pressure, sedation) and the next clozapine dose may be postponed or adjusted accordingly. For instance, in case of low blood pressure, a patient may temporarily be continued on half his/her normal dose.

After a treatment break exceeding 48 hours, clozapine should be re-titrated. If it is decided in advance to stop clozapine during surgery (and recovery) for more than 48 hours, it is advised to gradually reduce the dose, as abrupt withdrawal can lead to fast rebound psychosis.[5–7] and cholinergic rebound.[1] If the treatment break exceeds 72 hours, ZTAS needs to be notified and the blood monitoring frequency may have to be adapted thereafter following the guidelines in the ZTAS Manual.[8]

All decisions regarding therapy (dis)continuation, dose adjustments, *etc*. are clinical decisions, made at the discretion of the treating consultant.

Clearly, because many side effects such as hypotension, sedation and tachycardia are most prominent during clozapine titration it would not be advised to undergo surgery during clozapine titration. For similar reasons, surgery should probably also be avoided during the first 3 months of clozapine treatment, when possible.

Literature reports

There are a handful of case reports of patients who underwent surgery while on clozapine. Doherty *et al*.[9] present a case of a successful emergency caesarean section in a schizophrenic patient on clozapine treatment. Donnelly *et al*.[3] and John *et al*.[10] both report on cases of clozapine-associated hypotension during or after anaesthesia, which were refractory to first line epinephrine (see further below).[3,10] In the first of the two, a dose of clozapine was given 90 minutes before surgery together with 3 mg of lorazepam, which probably led to peak levels of these drugs during surgery, both contributing to CNS depression and hypotension.[3] In the second report, clozapine was also taken preoperatively, although no timeframe is mentioned.[10]

In a conference abstract by Leung *et al*. [11] the authors report on a case of unresponsiveness and hypoxemia after a total hip arthroplasty. The patient turned out to have elevated clozapine plasma levels, which was also corroborated by having increased hypersalivation. This may be an illustration of pharmacodynamic interactions leading to severe sedation and respiratory depression, when clozapine is present at high levels during and after anaesthesia.[11]

A case report by Geeraerts *et al*.[12] discusses the delayed recovery after short-duration, general anaesthesia with volatile agents desflurane and nitrous oxide in a patient on clozapine. The patient received his last clozapine dose 9 hours before anaesthesia was induced. The authors hypothesise that clozapine and desflurane may have synergised in their CNS depressive actions by their effects on dopaminergic neurotransmission.[12]

Risk management when using clozapine during surgery

Some general considerations include:

- There may be pharmacodynamic and pharmacokinetic interactions between clozapine and certain anaesthetics. These are addressed in detail further below.

- Many patients take other psychotropic drugs besides clozapine, which could produce significant interactions. Examples of important interactions are:
  - enflurane may precipitate seizures in patients taking tricyclic antidepressants[13]
  - pethidine may precipitate fatal 'excitatory' reactions in patients taking MAOIs and may cause serotonin syndrome in patients taking SSRIs[13]

- Major procedures induce profound physiological changes, which include electrolyte disturbances and the release of cortisol and catacholamines.[13]

- As smoking is prohibited in most hospitals, hospitalisation may lead to smoking cessation or reduced smoking. This can result in increased clozapine plasma levels.[14–16] E-cigarettes or nicotine patches do not circumvent this effect. Monitoring clozapine plasma levels is advised and dose reductions may be appropriate (see also Zaponex fact sheet "Clozapine metabolism and plasma level monitoring").

- Clozapine may delay recovery after short-duration, general anaesthesia.[12]

Table 1. ***Some of the risks of clozapine during and after surgery***	***Management***
Risk of plasma level changes due to pharmacokinetic interactions with anaesthetics or antibiotics	Take plasma levels prior to surgery. Monitor plasma levels in case of high pre-existing levels; monitor the patient for symptoms of toxicity; consider reducing the dose temporarily
Smoking is prohibited in most hospitals and smoking cessation can lead to increased clozapine plasma levels. E-cigarettes or nicotine patches do not circumvent this.	Monitor plasma levels, monitor the patient for symptoms of toxicity, consider reducing the dose temporarily
Risk of pharmacodynamic interactions such as hypotension, respiratory depression and sedation	Avoid high clozapine plasma levels. Alpha-adrenergic agents should be avoided to treat hypotension, because of the reverse epinephrine effect. Avoid giving a dose of clozapine within 12 hours prior to the operation
Increased risk of seizures	Avoid high clozapine plasma levels
Increased risk of developing constipation or paralytic ileus	Consider prophylactic laxatives, especially for high risk patients
Increased risk of venous thromboembolism	Consider prophylactic anticoagulation for high risk patients
Delayed recovery after surgery[12]	Avoid high clozapine plasma levels

Possible pharmacodynamic interactions of clozapine during and after surgery

CNS depression, respiratory depression and hypotension
As mentioned before, the main risks of clozapine during surgery are probably CNS depression (*e.g.* sedation), respiratory depression and hypotension, since almost all anaesthetic drugs can also cause a certain level of these effects. People undergoing general anaesthesia are probably at increased risk of respiratory depression, especially at high doses of clozapine.

Treatment of intraoperative hypotension
Clozapine may reverse the pressor effect of epinephrine ("reverse epinephrine effect"). Epinephrine use should therefore be avoided in the treatment of drug-induced hypotension while on clozapine.[1,10,13] John *et al*. report a case in which low-dose vasopressin was successfully used as a "rescue" therapy treating severe intraoperative hypotension refractive to alpha-adrenergic agents.[10] They further advise that anaesthetic management strategies should focus on minimising the need for compensatory autonomic responses to anaesthetic medications or techniques. Direct-acting vasoconstrictors should be immediately available, especially when general and major conduction anaesthesia techniques are being used. Arterial catheter placement and additional large-bore intravenous access should be considered in those with limited tolerance to hemodynamic instability. The placement of a central catheter to infuse potent vasoconstrictors also may be prudent in selected cases.[10]

Seizures
Certain anaesthetics may reduce the seizure threshold. Clozapine also increases the risk of seizures and especially patients with high clozapine levels may therefore be at increased risk of developing a seizure during or after surgery, although there is no literature to substantiate this assumption.

Gastrointestinal hypomotility
Postoperatively, surgical stress and some agents used in anaesthesia often lead to gastric or gastrointestinal stasis.[13] Postoperative morphine could also attribute to this. Oral absorption of medication may be compromised by this stasis.[13] In addition, since constipation is a common side effect of clozapine, the risk of developing paralytic ileus may be increased. In addition, low mobility due to bed rest after surgery can attribute to reduced gastric motility. The use of prophylactic laxatives may be considered, especially in patients who are known to be susceptible to constipation, or who are at increased risk for instance due to older age or pour nutritional status,[17] or who had abdominal or bowel surgery.

Anticholinergic effects
Anticholinergic agents are sometimes used in certain surgical procedures. Anticholinergic effects can be enhanced by the anticholinergic actions of clozapine, leading to the increased risk of anticholinergic side effects such as constipation or urinary retention.

Venous thromboembolism
Surgery can increase the risk of venous thromboembolism, which is positively correlated to the duration of surgery.[18] Since clozapine may also be associated with thromboembolism,[1] this should be considered an extra risk factor for the occurrence of thromboembolism. Consider prophylactic anticoagulation for high risk patients.

Aspiration pneumonia
Aspiration pneumonia is relatively common after general anaesthesia. Risk factors for aspiration pneumonia include aspiration, sedation and dysphagia.[19] Aspiration of ingested foods, dysphagia and sedation are all listed side effects of clozapine[1] and may theoretically contribute to the risk of aspiration pneumonia.

Obviously, locally (topically or subcutaneously) applied anaesthetics, usually pose lower risks as they have limited systemic effects.

Possible pharmacokinetic interactions of clozapine and anaesthetics, and antibiotics

Besides pharmacodynamic interactions, some pharmacokinetic interactions may also be expected, possibly leading to altered effects of the anaesthetics or increased clozapine plasma levels. Of course, these effects are temporary and the clinical significance may therefore be limited. The effect, however, may be taken into account in patients who already have high clozapine plasma levels.

Local and regional anaesthetics
Chloroprocaine, amethocaine, tetracaine, cocaine and procaine are amino esters, which are metabolised by plasma cholinesterase. As clozapine is mainly metabolised by liver cytochrome enzymes and amino esters are not, it is not expected that the use of amino esters affects clozapine plasma levels.

The aminoamides (lidocaine, prilocaine, mepivacaine, bupivacaine, ropivacaine, etidocaine) are mainly metabolised by the liver. The main enzymes involved in the metabolism of aminoamides are hepatic cytochrome (CYP) enzymes CYP1A2 and CYP3A4.[20] Clozapine is metabolised mainly through CYP1A2, but CYP3A4 is also involved.[21,22] Thus, aminoamides may compete with clozapine for metabolism through CYP1A2 (and CYP3A4), potentially increasing the levels of both clozapine and aminoamides, particularly in case of saturated clozapine metabolism. If inhibitors of CYP1A2 and CYP3A4 such as fluvoxamine,[23,24] ciprofloxacin[25] or erythromycin[26] are used concurrently, this risk may increase.

Volatile and gaseous anaesthetics
Most volatile and gaseous anaesthetics used nowadays are eliminated in unchanged form by exhalation.[20] The remainder is metabolised in the liver mainly by CYP2E1, which is not implicated in clozapine metabolism.

Antibiotics
Certain antibiotics, such as ciprofloxacin,[25] erythromycin[26] and isoniazid[27] have the potential to increase clozapine plasma levels. In contrast, rifampicin can severely reduce clozapine plasma levels.[28–30]

Management: Avoid high plasma levels

If it is decided to continue clozapine during surgery, it appears sensible to avoid high clozapine levels. High plasma levels can increase the risk of CNS depression, respiratory depression, hypotension, and seizures, and patients are probably more vulnerable to these effects during and after surgery. Patients who smoke are at increased risk, as smoking cessation or reduced smoking during hospitalisation can further enhance clozapine levels. In addition, infection can increase clozapine plasma levels (see also Zaponex fact sheet “Clozapine metabolism and plasma level monitoring”). Certain anaesthetics or antibiotics may also enhance plasma levels.

It is advised to do a plasma level assay for each patient before surgery. In case of high preoperative clozapine levels, consider (temporarily) reducing the dose and monitor the patient for signs of toxicity such as severe sedation, tachycardia, hypersalivation or hypotension. If possible, monitor the clozapine plasma level further during hospitalisation, especially in patients at increased risk.

Swallowing difficulties, feeding tubes and clozapine tablets

Some patients have swallowing difficulties after surgery and can ingest only liquids. Also, patients sometimes receive a percutaneous endoscopic gastrostomy (PEG) or a nasogastric feeding tube after surgery. For such patients, taking their clozapine tablets will be a problem.

Zaponex tablets are developed for direct oral administration. However, in clinical practice, we are aware that tablets are sometimes crushed and placed in a liquid to facilitate their intake in certain circumstances, either orally or via a gastric feeding tube. This is acceptable when the crushing is performed immediately before the dosing. The tablets are immediate release, are not film coated and are not in the form of a matrix.

If the tablets are to be dispersed in fluid, we would recommend that the glass is rinsed afterwards with cold fluid and the contents are consumed by the patient to ensure that the full dose has been taken. Clozapine does not dissolve in water, it remains a suspension. Therefore, oral ingestion should take place soon after the mixture is stirred, since it is not known how long the suspension remains stable. A

substance such as yoghurt, cold pudding/custard, jam, etc. may also be suitable to mix the crushed tablets with, as long as it is made sure that the full dose is taken.

We cannot recommend mixing the tablets with hot drinks such as tea or coffee, as the patient would not be able to swallow the liquid immediately and hot temperatures may affect the active ingredient.

For long-term use, a premade liquid preparation may be more appropriate. A pre-made clozapine solution (specialty), which does not need to be shaken, can be obtained from St. Georges Hospital in London. ZTAS can provide further information on this formulation on request.

Advice for daily practice:

- Literature provides too little scientific back-up for an evidence-based guideline
- Each patient requires an individual assessment whether or not clozapine should be stopped during surgery

When continuing clozapine:

- Be aware of pharmacodynamic and pharmacokinetic interactions between clozapine and anaesthetics
- The main pharmacodynamic interactions are probably CNS depression (*e.g.* sedation), respiratory depression and hypotension
- Because of these interactions, it is probably sensible to avoid giving a dose of clozapine within 12 hours prior to the operation
- High clozapine levels should be avoided during surgery
- Smoking cessation during hospitalisation may significantly increase clozapine plasma levels
- It is advised to take plasma levels before surgery and if possible, during recovery. Dose reductions may be needed
- Consider if prophylactic anticoagulation or laxatives are necessary

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