Zaponex Fact Sheet
Fever

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

SmPC statement

The Summary of Product Characteristics for Zaponex® (section 4.4) states: "During clozapine therapy, patients may experience transient temperature elevations above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered."[1]

Causes of fever

Fever can be associated with a range of clozapine-related and -unrelated processes. Fever may be a primary, transient and benign episode during clozapine titration, but in rare cases, fever can be associated with NMS or agranulocytosis (Table 1). In addition, fever can be one of the symptoms of myocarditis or other (very) rare inflammatory disorders associated with clozapine, including pericarditis, hepatitis, pancreatitis, (eosinophilic) colitis, acute interstitial nephritis, (poly)serositis, and lupus-like syndrome (Table 1).

Obviously, fever and flu-like symptoms can also be signs of bacterial or viral infections, or other (inflammatory) conditions unrelated to clozapine.

Table 1. Clozapine-associated syndromes characterised by fever

Condition	Symptoms	Diagnostic testing
Benign and transient fever during clozapine titration	Asymptomatic, moderate fever	Diagnosis by exclusion
Neuroleptic malignant syndrome (NMS)	(High) fever, muscular rigidity, autonomic instability, changes in consciousness, diaphoresis	Creatine phosphokinase (CPK), WBC counts[2]
Agranulocytosis/neutropenic fever	Flu-like complaints such as fever or sore throat	Neutrophil counts
Myocarditis	Persistent tachycardia at rest, palpitations, arrhythmias, flu-like symptoms, fever, chest pain, fatigue, dyspnoea, tachypnoea	Troponin, CRP, ECG, echocardiogram, MRI
Pericarditis/pericardial effusion	Fever, tachycardia, chest pain, shortness of breath, cough	CRP, echocardiogram
Hepatitis	Abdominal pain, flu-like complaints, malaise, fatigue, jaundice, dark urine,	Liver function tests (LFT)

	oedema, nausea, vomiting and/or anorexia	
Pancreatitis	Abdominal pain, nausea, vomiting	Amylase, lipase, abdominal ultrasound
Eosinophilic colitis	Abdominal pain, fever, diarrhoea, weight loss	Eosinophil counts, endoscopy, colonic biopsy
Acute interstitial nephritis	Skin rash, fever, tachycardia, dysuria, arthralgia	Serum creatinine, eGFR, CRP, proteinuria
Polyserositis	Fever/flu-like symptoms, chest pain, dry cough, shortness of breath/tachypnoea, tachycardia, gastrointestinal symptoms[3]	Imaging tests and exclusion of other diagnoses
Lupus-like syndrome	Fever, myalgia, arthralgia, serositis	Positive ANA test with one clinical symptom

Benign transient fever

Clozapine is an antipsychotic agent with immunomodulatory effects, so clozapine-induced fever and benign transient hyperthermia are common side effects of clozapine therapy. Fever typically occurs within the first 10-15 days of treatment and lasts on average 2 to 4 days.[4] Clozapine-induced fever has been associated with a titration rate of more than 50 mg per week, concomitant use of valproate, and the presence of physical illnesses.[5]

The estimated incidence of fever during clozapine therapy varies between 0.5-55%.[6–8] This large disparity is probably due to discrepancies in study methodology, including the definition of fever.[4] There is no clear evidence suggesting certain patient groups are at increased risk of developing fever, although there is some indication that the incidence is higher in older patients.[9] The presence of fever during clozapine therapy does not appear to predict agranulocytosis, NMS, or an increased rate of drug discontinuation after 1 year.[4]

The mechanism of clozapine-induced fever is unclear. A classic allergic reaction seems to be unlikely, since it has been shown that patients who experienced fever during first clozapine initiation and consequently discontinued therapy, did not experience the same reaction during re-challenge.[4] However, the immunomodulatory effects of clozapine are likely to play a role in the onset of clozapine-induced fever.[10]

A number of plausible explanations for the induction of fever exist, including the implication of a immune-modulating effect through cytokine release. Due to its small size, clozapine can trigger a pro-inflammatory response by causing increased cytokine production, which is associated with antibody-mediated hypersensitivity reactions.[11,12] Studies have shown that introduction of clozapine in patients can (temporarily) increase the levels of C-reactive protein (CRP)[13], as well as pro- and anti-inflammatory cytokines such as soluble tumour necrosis factor (TNF) receptor p55, p75, granulocyte colony-stimulating factors (G-CSF), and soluble interleukin-2 (IL2) receptor.[12,14,14–19] IL-6 might also have a specific role in this.[19]

Fever often occurs concurrently with elevations in several cell lines (including neutrophils, monocytes, basophils, platelets and eosinophils), supporting the notion of an inflammatory process where cytokine changes precipitate transient occurrences of hyperthermia and increased leucocytes.[11,13–15]

Benign causes of fever are much more frequent than life-threatening adverse drug reactions (ADR) during clozapine treatment. Discontinuation should not be considered as automatic in the event of fever, especially during the early phase of clozapine initiation.[20]

Agranulocytosis/neutropenic fever
Agranulocytosis is a well-known side effect of clozapine, with an estimated incidence varying from 0.38-0.8 %.[21–24] Agranulocytosis most commonly occurs between the start and 18 weeks following initiation of treatment[1], but typically between weeks 6 and 18.[24] Neutropenia or agranulocytosis accompanied by fever is a medical emergency and requires immediate specialty care. Other symptoms may include sore throat or other signs of infection.[1] As the white blood cell counts are carefully monitored during clozapine use, clozapine-induced agranulocytosis seldom develops unnoticed. More information on this condition can be found in the Zaponex fact sheet "Agranulocytosis and neutropenia" which can be obtained via the ZTAS website.

Neuroleptic malignant syndrome (NMS)
Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic, potentially life-threatening complication known to occur during therapy with dopamine receptor antagonists.[2] Apart from fever, symptoms typically include severe muscular rigidity, autonomic instability, changes in the level of consciousness, diaphoresis, increased creatine phosphokinase (CPK) and leukocytosis.[2] NMS often develops within 30 days following initiation of antipsychotic treatment.[25] The clinical course typically begins with muscle rigidity, followed by a fever within several hours of onset, as well as mental status changes that can range from mild drowsiness, agitation or confusion to a severe delirium or coma.[26] If the diagnosis of NMS is confirmed, clozapine should be discontinued immediately and appropriate medical measures should be administered.[1] More information about clozapine-induced NMS can be found in the Zaponex fact sheet "Neuroleptic malignant syndrome" which can be obtained via the ZTAS website.

Myocarditis
Myocarditis is a rare side effect of clozapine, usually occurring within the first month of clozapine therapy[27,28], but it may occur at any time.[1,27,29] Although not always present[28], fever and flu-like symptoms can also be symptoms of clozapine-associated myocarditis. Other symptoms include persistent tachycardia at rest, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (*e.g.* unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction.[1] More information about myocarditis can be found in the Zaponex fact sheet "Myocarditis and cardiomyopathy" which can be obtained via the ZTAS website.

Toxic hepatitis
Clozapine-induced hepatitis is a rare side effect of clozapine therapy[1], with an estimated incidence of 0.06%.[30] Clozapine-induced hepatitis can be accompanied by fever, abdominal pain, malaise, fatigue, anorexia, nausea, vomiting, skin rash, eosinophilia, jaundice and/or pleural effusion.[30–41] For further information and management see the Zaponex fact sheet "Liver function" which can be obtained via the ZTAS website..

Pancreatitis
Pancreatitis is a rare side effect of clozapine therapy.[1] Clozapine-induced pancreatitis is sometimes asymptomatic[42–44], however in most cases, it is accompanied by fever, abdominal pain, nausea and/or vomiting.[45–49] Amylase and lipase measurements, as well as abdominal ultrasound can be used to confirm the diagnosis.

Eosinophilic colitis
In literature, several cases of clozapine-induced eosinophilic colitis have been reported.[50–52] Eosinophilic colitis is characterised by fever, eosinophilia, abdominal pain, diarrhoea and/or weight loss, and can only be diagnosed by endoscopy and histological analysis of colonic mucosal biopsies.

Acute interstitial nephritis
Acute interstitial nephritis is a very rare side effect of clozapine[1], mostly occurring very early in treatment (within 2-3 weeks following initiation).[53] Proteinuria and/or white blood cells in the urine may be the earliest indicators of acute interstitial nephritis/acute renal failure.[53] Other symptoms of acute interstitial nephritis include fever, skin rash, tachycardia, arthralgia, dysuria, elevated IgE, estimated glomerular filtration rate (eGFR) decline, increased serum creatinine and CRP. If this condition is suspected, it is important that antibiotics are avoided since they are often nephrotoxic. If fever is directly interpreted as a sign of infection and an antibiotic is prescribed (without clear evidence of infection), antibiotics may exacerbate nephritis.[53–55] For further information and management, see also the Zaponex fact sheet "Renal and urinary disorders" which can be obtained via the ZTAS website.

(Poly)serositis
A few dozen literature publications have linked clozapine therapy with serositis, inflammation of serous membranes that can lead to local effusion. The pericardium was most often affected in these reports (elaborated on in the next paragraph), but the pleura[56] and/or multiple serous membranes can also be involved (polyserositis).[3,57–62]

Pericarditis/pericardial effusion
Pericarditis/pericardial effusion is a rare side effect of clozapine.[63] Clozapine-induced pericarditis may develop from 9 days to 7 years after clozapine initiation, but with a higher probability during the up-titration phase and in the first 5-6 weeks from its introduction. The presentation of clozapine-induced pericarditis may range from a nearly asymptomatic clinical picture (i.e., mild flu-like symptoms and elevated pro-inflammatory indices) up to fulminating cardiomyopathy resulting in death.[64] Based on data provided by mainly case reports, clozapine-induced pericarditis can be accompanied by fever, tachycardia, chest pain, shortness of breath, cough, pleural effusion, gastrointestinal disturbances, CRP elevations and/or eosinophilia.[59,60,65–69] The electrocardiogram (ECG) may be unaffected.[65,67] Effusions can be observed by X-ray, but pericarditis is usually confirmed by echocardiography.[70] In most reported cases, discontinuation of clozapine treatment resulted in complete resolution of symptoms.

Lupus-like syndrome
Drug-induced lupus presents as a syndrome similar to systemic lupus erythematosus. Clinical features are highly variable, but generally include fever, myalgia, arthralgia, serositis, and a positive antinuclear antibodies (ANA) test. Although clozapine is not amongst the drugs typically associated with this syndrome, six case reports have been published describing clozapine inducing a lupus-like syndrome. In the majority, the syndrome resolved following clozapine cessation[71–73] and treatment with nonsteroidal anti-inflammatory drugs[74] or corticosteroids.[75] However, in one case, rechallenge was without success.[76]

Infection
Of course, fever can also be a symptom of bacterial or viral infections. If an infection is diagnosed, it should be treated accordingly. Clozapine therapy may be continued, depending on the clinical situation.

Note that it has been reported that infections increase plasma clozapine levels[77–81], by suppression of CYP1A2 which is the main clozapine-metabolising enzyme.[81,82] Consequently, extra care needs to be taken during infection to prevent possible clozapine toxicity, and it is advisable to perform a clozapine plasma level assay.

Certain antibiotics should be avoided for the treatment of infections because of pharmacodynamic or pharmacokinetic interactions. For instance, ciprofloxacin[83], isoniazid[84] or possibly erythromycin[85,86] can

increase clozapine plasma levels, while rifampin[1,87–89] reduces plasma levels. In addition, many antibiotics have a propensity to cause neutropenia or leukopenia. It is advisable to check the incidence rates for haematological adverse events of the contemplated antibiotic. Chloramphenicol, sulfonamides, dapsone, (benzyl) penicillin G, rifabutin and voriconazol are among the group with the highest risk of developing neutropenia or leukopenia. These drugs may be contraindicated when used in combination with clozapine. Please contact ZTAS for specific advice.

Management

When fever occurs, it is critical to differentiate benign fever from serious conditions such as agranulocytosis, NMS or myocarditis. If the patient also has eosinophilia, this may be a reason to be extra vigilant, since eosinophilia is often co-reported with the early inflammatory syndromes, such as myocarditis, pericarditis, hepatitis, pancreatitis, eosinophilic colitis or acute interstitial nephritis (see fact sheet Eosinophilia which can be obtained via the ZTAS website).[90]

In addition, infection should be ruled out. The presence of an infection can be determined via general diagnostic tools such as CRP measurement, urinalysis, chest X-rays and blood cultures. ZTAS advises twice weekly blood monitoring when patients exhibit signs of infection.

When a patient has a raised temperature, a full blood count with differential should always be performed to rule out the possibility of an underlying neutropenia.[1] However, if the fever presents within the first 3 weeks following clozapine initiation, it is less likely to be caused by neutropenia, as the incidence of neutropenia usually peaks later in treatment.[24] If the patient indeed exhibits lowered neutrophil counts, the standard Zaponex ‘amber’ or ‘red’ procedures must be followed.[1]

Other possible causes of fever should also be investigated.[90,91] Clinicians should be vigilant for the clozapine-induced medical conditions that have been co-reported with fever mentioned in Table 1, as well as the diagnostic tests to exclude these (very) rare side effects. If NMS, myocarditis, pericarditis, hepatitis, pancreatitis, colitis, acute interstitial nephritis, (poly)serositis or lupus-like syndrome is suspected, clozapine should be discontinued and the patient treated accordingly.[4] More information on these conditions and their diagnosis can be found in the fact sheets “Neuroleptic malignant syndrome”, “Neutropenia and agranulocytosis”, “Myocarditis and cardiomyopathy”, “Liver function”, “Renal and urinary disorders” and “Eosinophilia” which can be obtained via the ZTAS website.

Note that patients suffering from the above conditions will not always display all of the symptoms listed. It is therefore important to keep these patients under close clinical observation and to be aware of additional symptoms.

If there is no other cause apparent that could induce fever and if the fever is moderate, treatment with clozapine may continue.[4] As fever is associated with fast titration, it may be considered to slow down clozapine titration.[5] Alternatively, temporary clozapine dose reductions may alleviate fever. Also, antipyretic drugs, *e.g.* paracetamol, are suggested to give some relief.[4]

If the fever is high and/or persistent, clozapine may be withheld until the fever diminishes.[4] Note that if treatment is discontinued for more than 48 hours, the dose needs to be re-titrated.[1] Any decision regarding treatment (dis)continuation is at the discretion of the treating consultant.

Advice for daily practice:

- Benign causes of fever are much more frequent than life-threatening adverse drug reactions during clozapine treatment. Discontinuation should not be considered as automatic in the event of fever, especially during the early phase of clozapine initiation
- In case of fever, eliminate the possibility of:
  - Agranulocytosis/neutropenia
  - Neuroleptic malignant syndrome (NMS)
  - Myocarditis
  - Pericarditis/pericardial effusion
  - Hepatitis
  - Pancreatitis
  - Eosinophilic colitis
  - Acute interstitial nephritis
  - (Poly)serositis or lupus-like syndrome
  - Infection
- If serious causes can be excluded, clozapine therapy may be continued
- Slow dose titration or temporary dose reductions may ameliorate clozapine-induced fever
- The use of paracetamol may give some relief
- In case of high and persistent fever, clozapine may be withheld until the fever diminishes

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