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Review article

Clozapine induced gastrointestinal hypomotility: A potentially life threatening adverse event. A review of the literature

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ABSTRACT

Objective: The haematological and cardiac complications of clozapine have been well documented. Recent evidence from pharmacovigilance databases suggests that gastrointestinal (GI) complications are the leading cause of clozapine related deaths. This review aims to describe clinical features along with preventative and treatment options.

Method: A review of MEDLINE via PubMed searching for all articles published up to February of 2016. Inclusion criteria were articles that provided clinical or epidemiological information relating to the diagnosis, outcome, management or pathophysiology of clozapine related gastrointestinal disorders in humans.

Results: Three large case series were identified with 104 cases, 20 of these reported clinical details. A further 52 cases reports were included. Median age was 40, with 79% being male, mean daily clozapine dose was 453 mg. Mortality was 38% with survivors being younger (39 vs. 42), on lower daily doses (400 mg vs. 532 mg), more likely to be female (32% vs. 6%). Four patients were re-challenged with clozapine following CIGH, two suffered a recurrence.

Conclusion: Risk factors for CIGH appear to be older age, male gender, patients in the first four months of treatment, co-prescription of constipating agents, higher daily dose of clozapine, and previous CIGH. Risk factors for death were older age and male gender. Patients receiving clozapine should be counselled about the dangers of constipation and to report new GI symptoms. Once severe CIGH has occurred clozapine should be halted and reviewed with bowel symptoms managed promptly. Re-challenging with clozapine may present substantial risks due to the severity of CIGH and a paucity of evidence. From the available evidence a treatment strategy has been proposed. Further prospective data regarding CIGH are needed to allow a better assessment of the scale of the problem with the development and testing of treatment strategies.

Contents

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1. Introduction

Schizophrenia affects approximately 1% of the world's adult population [1]. The most effective agent for the treatment of schizophrenia is clozapine and is particularly efficacious in cases of treatment-resistant schizophrenia [2–4]. Clozapine is the only antipsychotic medication with a proven reduction in mortality by reducing the rate of suicide. It also has few or no extrapyramidal symptoms, which occur with other antipsychotics [5,6].

The reluctance to use clozapine is based on its serious adverse effects including: fatal agranulocytosis, cardiotoxicity, seizures and clozapine induced gastrointestinal hypomotility (CIGH). The severity of CIGH is under appreciated. CIGH is the leading cause of clozapine related death in a review of pharmacovigilance data in New Zealand [7]. Clozapine has the strongest anti-muscarinic effects of any neuroleptic, which may explain why it is so strongly associated with death from constipation [8–10].

CIGH is a paralytic ileus leading to a clinical condition similar to bowel obstruction. The lack of peristalsis rather than mechanical obstruction impedes forward movement of gastrointestinal contents. Paralytic ileus causes constipation and retention of gas and fluid raising intraluminal pressure reducing mucosal perfusion [11]. If systemic blood pressure drops, adequate perfusion to gastrointestinal mucosa is not maintained leading to loss of mucosal integrity and bacterial invasion causing sepsis [11,12]. Agents with anti-adrenergic effects, like clozapine, could cause periods of hypotension that, combined with increased intraluminal pressure, lead to mucosal breakdown [11]. Once a paralytic ileus has developed it leads to intravascular depletion and further exacerbating ischaemia [13]. It has been also suggested that anti-serotonergic effects of clozapine reduce nociception from the bowel leading to reduced symptoms and signs of distress, thus potentially delaying diagnosis [14,15]. Proposed factors that cumulatively contribute to CIGH are summarised in Fig. 1 [11–20].

The objective of this review is to describe the presenting features and outcomes of patients suffering from CIGH. This review aims to raise awareness of this condition and provide some guidance on management strategies that can be adapted as more evidence becomes available.

2. Method

A review of MEDLINE via PubMed searched for all articles published up to 5th January 2013 and repeated 24th February 2016. The search criteria included: MESH/keyword terms clozapine with MESH terms intestinal diseases or signs and symptoms, digestive. Other keywords included: clozapine, Clozaril, ileus, megacolon, necrosis, obtundation, motility, dysmotility, bowel, obstruction, colon*, gastrointestinal, gastro*, constipation, enterocolitis, colitis, obstipation, pseudoobstruction. Another area of interest was studies of patients who died on clozapine, to see if there were gastrointestinal causes listed. A second search of MEDLINE via Pubmed was undertaken with the keyword terms clozapine or Clozaril, in conjunction with the terms death or fatal. There were no limits placed,

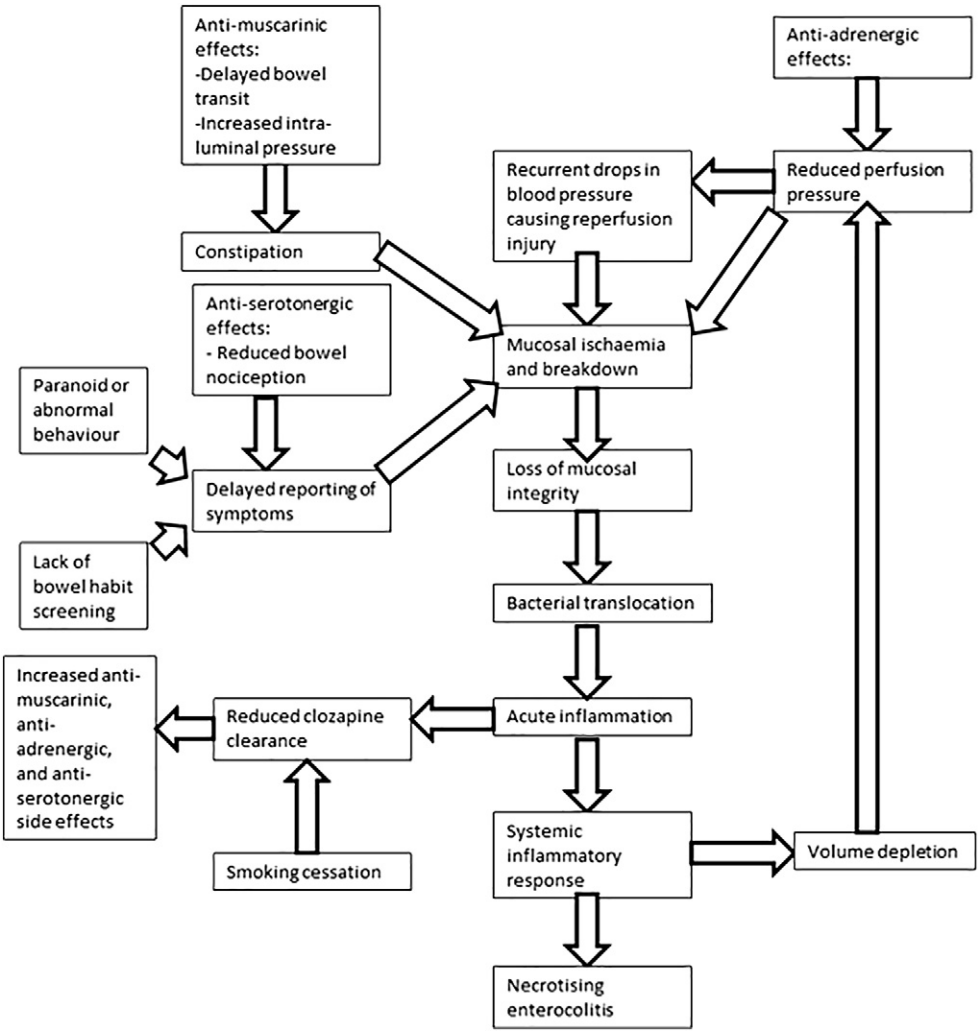

Fig. 1. Multiple contributors that cumulatively heighten the risk of clozapine induced gastrointestinal hypomotility (CIGH) [11–20].