WHAT IS THE EFFECT OF PROTON PUMP INHIBITORS ON THE SOLUBILITY OF CLOZAPINE?

Reema H S Sulthan[1], Victoria C Wing[2,3], Parag Roy[4], Timothy Donaldson[2], Oisín N Kavanagh[4]

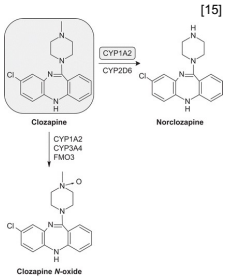
School of Medicine, Newcastle University, UK[1], Cumbria Northumberland Tyne and Wear (CNTW) NHS Trust, UK[2], Translational Clinical Research Institute, Newcastle University, UK[3], School of Pharmacy, Newcastle University, UK[4] | ✉ r.hameed-sulthan2@newcastle.ac.uk

INTRODUCTION & AIMS

Clozapine (CLZ) is the drug of choice for treatment-resistant schizophrenia, with serum concentrations linked to both efficacy and side effects. Patients on CLZ often experience gastrointestinal issues [1], prompting the use of proton pump inhibitors (PPIs). As a weak base (pKa ≈ 7.2), CLZ's solubility is strongly pH-dependent.

As CLZ primarily undergoes metabolism by CYP enzymes, existing literature often emphasises hepatic interactions with PPIs, neglecting the simpler relationship relating to pH and solubility. We propose that elevated gastric pH may reduce the solubility of CLZ, thereby impairing absorption and further lowering its bioavailability.

[15]

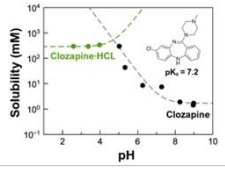


AIMS

- Investigate the effect of pH on the solubility of CLZ using laboratory studies
- Review current literature to:
  - Identify the effects of common PPIs on intragastric pH
  - Determine the impact of different PPIs on CLZ plasma concentrations
  - Evaluate the effect of cytochrome (CYP) P450 activity and genotype on CLZ plasma concentrations

CLOZAPINE SOLUBILITY STUDIES

CLZ is formulated as a hydrochloride salt to enhance solubility, but the balance between soluble and less soluble forms is pH-dependent. [16] We investigated this by conducting experiments to generate a solubility curve. As the protonated hydrochloride salt, CLZ was highly soluble under acidic conditions, but its solubility decreased markedly as the pH approached neutrality and exceeded the pKa.



PPIs & INTRAGASTRIC pH

PPIs have varying effects on raising and maintaining intragastric pH.

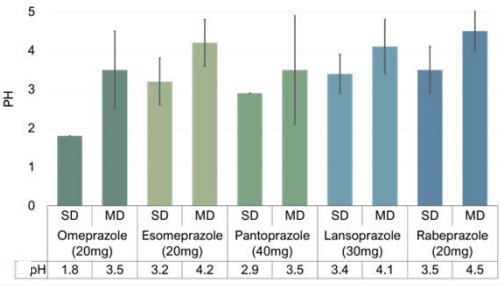
However, direct potency comparisons should be made with caution due to differing standard doses.

Table 1: Summary of the PPI's Effect on Gastric pH [2-5]

PPI	Onset of Action	Duration of Effect
Omeprazole	Slower	Less sustained
Esomeprazole	Fast	Excellent
Pantoprazole	Medium	Good
Lansoprazole	Medium	Good
Rabeprazole	Rapid	Excellent

Figure 1: Intragastric pH ± Standard Deviation at Standard Doses [3]

Data comparing the mean 24-hour pH in healthy volunteers after a single dose (SD) of common PPIs to the mean pH under steady-state conditions after multiple days of the same dosage (MD).



PPIs & CLOZAPINE CONCENTRATION

OMEPRAZOLE

Study 1 [6]
Omeprazole co-medication reduced clozapine plasma concentrations by 41.9% and 44.7% in two individuals.

Study 2 [7]
Switching from omeprazole to esomeprazole resulted in a 296% increase in clozapine plasma levels within 2 days.

In both studies, these changes were initially attributed to the induction of CYP1A2 or other cytochrome P450 alterations from the PPI. However, the rise in gastric pH from omeprazole cannot be ignored.

In Study 2, the rapid change is difficult to reconcile with the slow reversal of CYP expression induction caused by omeprazole. [8] Possible explanations include an underlying infection quickly causing cytokine-mediated CYP suppression [9], or increased drug absorption due to rebound acid hypersecretion. [10]

PANTOPRAZOLE

Study 3 [11]
Adding pantoprazole to clozapine treatment did not significantly affect clozapine levels.

In non-smokers, pantoprazole slightly reduced CLZ levels, consistent with reduced absorption at higher gastric pH. In smokers, CLZ levels increased slightly.

As pantoprazole causes a smaller rise in gastric pH, the solubility of CLZ may not be substantially affected. These findings, derived from small sample sizes, should be interpreted with caution.

RABEPRAZOLE

Study 4 [12]
Switching between rabeprazole and omeprazole did not consistently affect the norclozapine/clozapine ratio or overall clearance.

Omeprazole and rabeprazole differ both in their effects on CYP enzymes and in the ways they are metabolized by them. [12] Yet, these comparable results suggest that CLZ's metabolism, influenced by multiple CYP isoforms, may exhibit metabolic redundancy. [13] However, the lack of an untreated control group limits definitive conclusions about the effect of either PPI on CLZ exposure.

CLOZAPINE & CYP POLYMORPHISMS

Although factors influencing the enzymes involved in CLZ's metabolism affect its plasma levels – e.g., CYP1A2 induction by smoking reducing CLZ concentrations – research shows that common CYP polymorphisms do not fully account for the substantial interindividual variability in CLZ exposure. Instead, ABCB1 gene variants may be the only ones to influence CLZ concentrations and clinical response. [13,14]

Table 2: Summary of Key Enzymes and Transporters Influencing CLZ Pharmacokinetics (PK) [13,14]

Enzyme/ Transporter	Relation to CLZ PK	Effect of Gene Polymorphisms on CLZ levels
CYP1A2	• Principal enzyme involved in metabolism • Strongly modulated by environmental factors	• Inconsistent and often minor • Small association with *1C and *1D alleles – higher levels
CYP2C19	• Secondary contributor to metabolism	• Poor-metaboliser status associated with higher levels
CYP3A4	• Contributes to metabolism when CYP1A2 activity is reduced	• Minimal Effect
CYP2D6	• Minimal involvement in metabolism	• Inhibition of activity may lead to raised levels
ABCB1	• Efflux transporter (GIT, kidney, liver, BBB)	• SNPs of 3435TT and 3435CC linked to altered levels

CONCLUSION

The activity of CYP enzymes surely plays a role in CLZ's pharmacokinetics. Still, we argue that other factors, such as changes in gastric pH and variations in first-pass metabolism, may contribute to its low bioavailability and significant interindividual variability more than we currently acknowledge.

Direct, high-quality evidence demonstrating that PPIs significantly reduce clozapine solubility or systemic exposure remains limited. Nonetheless, we may be approaching a pivotal moment in our understanding – perhaps it is time to expand our focus beyond the established context of CYP enzymes and explore this promising new area of research.

Northern Centre for Mood Disorders

NHS Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust

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