NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Oral Tetracycline and Fluoroquinolone Antibiotic Interactions with Multivalent Cation Containing Products, Management of

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

Version Number:	1
Does this version include changes to clinical advice:	N/A
Date Approved:	31st May 2023
Date of Next Review:	31st May 2026
Lead Author:	Rachael Rodger
Approval Group:	Antimicrobial Utilisation Committee

Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

Management of Oral Tetracycline and Fluoroquinolone Antibiotic Interactions with Multivalent Cation-Containing Products

1. Background

Concomitant oral administration of tetracycline and fluoroquinolone antibiotics (Table 1) with multivalent cation products (Table 2) can result in formation of insoluble chelation complexes in the gut and inhibition of antibiotic absorption. It is important to recognise and manage these interactions to prevent:

- **suboptimal antibiotic absorption and treatment failure**
- **unnecessary escalation to broader antibiotic cover including intravenous therapy**
- **development of antimicrobial resistance**

Serum levels of oral doxycycline can be reduced by as much as 90% to 100% by oral iron and ciprofloxacin plasma levels can be reduced by over 50% by the simultaneous administration of enteral feeds and oral nutritional supplements such as Ensure®.

In NHSGGC recent quality improvement work (n=283) has highlighted that over a third (34%) of hospital inpatients receiving a tetracycline or fluoroquinolone antibiotic are also co-prescribed an interacting multivalent cation-containing product at the same time and a high proportion (39%) of these patients are prescribed more than one multivalent cation-containing product. At discharge just over half (58%) of these interactions are appropriately managed. The most common antimicrobials potentially compromised by this interaction were doxycycline, ciprofloxacin and levofloxacin (Table 1) and the most common cation-containing products identified were oral calcium, oral iron and antacids (Table 2).

In addition, in line with NHSGGC Primary Care Empirical Antimicrobial Guidelines, a high proportion of fluoroquinolone and tetracycline antibiotics are initiated in primary care resulting in potential for common occurrence of these interactions in the primary care setting.

Document Author: Dr Rachael Rodger (Antimicrobial Pharmacist)

Document Prepared by: NHSGGC Antimicrobial Pharmacist Team and NHSGGC Antimicrobial Management Team

Document Approved by: NHSGGC Antimicrobial Utilisation Committee

Date Approved: May 2023 Review Date: May 2026

Table 1. Common examples of tetracycline and fluoroquinolone antibiotics

Tetracycline Antibiotics	Fluoroquinolone Antibiotics
Doxycycline Lymecycline Minocycline Tetracycline, Oxytetracycline	Ciprofloxacin Levofloxacin Norfloxacin Ofloxacin Moxifloxacin

Table 2. Common examples of oral multivalent cation products

Oral Multivalent Cation Products	
Iron e.g. ferrous fumarate, ferrous sulphate, ferrous gluconate, sodium feredetate	**Zinc e.g.** zinc sulphate, zinc sulphate monohydrate, zinc acetate
Calcium e.g. calcium carbonate, calcium gluconate, calcium lactate, calcium and vitamin D (Acrete D3, Adcal D3, Cacit D3, Calcichew D3, Calcichew D3 Forte)	**Antacids e.g.** sodium alginate with calcium carbonate and sodium bicarbonate (Peptac), co-magaldrox (Maalox), Bismuth subsalicylate (Pepto-Bismol)
Magnesium e.g. magnesium sulphate, magnesium glycerophosphate, magnesium aspartate, magnesium citrate, magnesium trisilicate, compound antacid formulations	**Enteral Feeds e.g.** Ensure, Ensure Compact, Ensure Shake, Ensure Plus, Fortisip, Fortisip Compact and Fresubin
Aluminium e.g. aluminium hydroxide, compound antacid formulations	**Sucralfate** **Phosphate Binders e.g.** Sevelamer, Lanthanum carbonate **Multivitamins & supplements** e.g Forceval

2. Interaction Management

When possible, multivalent cation-containing products should be **stopped/withheld** in patients receiving oral tetracycline or fluoroquinolone antibiotics until the antibiotic treatment course is complete. This should not be an issue for most short antibiotic treatment courses but for more prolonged antibiotic treatment courses **stopping/withholding** the cation-containing product will need greater clinical consideration.

If the cation-containing product **cannot** be **stopped/withheld**, then an **alternative antibiotic** should be considered. If necessary, contact an antimicrobial pharmacist, microbiologist or infectious diseases consultant for advice.

If there is no suitable alternative antibiotic and the tetracycline or fluoroquinolone and cation-containing product **must be prescribed together**:

- Administration times should be spaced apart as far as possible to improve antibiotic absorption (Table 3) and patients should be reviewed regularly for potential treatment failure. **Note**: doxycycline undergoes enterohepatic recycling which may reduce the effectiveness of dose spacing at preventing treatment failure.
- Consideration should be given to reducing the dose frequency of the multivalent cation-containing product for the duration of the antibiotic course to make dose spacing more manageable.
- In patients prescribed combined calcium and vitamin D supplements (e.g Acrete D3) requiring more prolonged tetracycline or fluoroquinolone treatment courses, consider switching from the combined product to vitamin D alone (e.g colecalciferol) until the antibiotic treatment course is complete.
- In the case of oral nutritional supplements, multiple sips throughout the day should be replaced by set administration times to enable adequate spacing from oral antibiotic administration (Table 3). If a patient is receiving a continuous cation-containing enteral feed administration of interacting tetracyclines/ fluoroqinolones should be avoided.

  Note: alterations to feeding regimens should be discussed with dietetic staff.

3. Co-administration with food and dairy products

Co-administration with food and dairy products can also compromise the absorption of some tetracycline and fluoroquinolone antibiotics. Refer to Table 3 for management advice.

4. Patient Information

Patients initiated on a fluoroquinolone or tetracycline antibiotic should be made aware of the need to avoid multivalent cation-containing products and should discuss the concomitant use of any over the counter medicines (e.g. multivitamins, antacids) with their doctor or hospital/community pharmacist/pharmacy technician. If applicable patients should be made aware of food and dairy restrictions and that H_2 receptor antagonists and proton pump inhibitors **do not** require to be spaced apart from oral tetracycline or fluoroquinolone antibiotics.

Table 3 Antibiotic and Multivalent Cation Interaction Summary and Suggested Management

Fluoroquinolones	Co-administration with multivalent cation-containing product* (see Table 2)	Co-administration with dairy products	Co-administration with food
Ciprofloxacin	Potential **50-90%** reduction in ciprofloxacin plasma levels. • **Stop/withhold** multivalent cation-containing product* until antibiotic course complete. • If cation-containing product* **cannot** be stopped/withheld consider alternative antibiotic**.** • If concomitant administration necessary dose space as far apart as possible and monitor for treatment failure.	**Avoid** concurrent administration with: • milk • yoghurt • calcium fortified orange juice for **2 hours before or after** antibiotic.	Absorption **not** significantly affected by food.
Norfloxacin	Potential **90%** reduction in norfloxacin plasma levels. • **Stop/withhold** multivalent cation-containing product* until antibiotic course complete. • If cation-containing product* **cannot** be stopped/withheld consider alternative antibiotic**.** • If concomitant administration necessary dose space as far apart as possible and monitor for treatment failure.	**Avoid** concurrent administration with: • milk • yoghurt • calcium fortified orange juice for **2 hours before or after** antibiotic.	Absorption **not** significantly affected by food.
Levofloxacin, **Ofloxacin,** **Moxifloxacin**	Potential **20-40%** reduction in antibiotic plasma levels. (**Note**: Calcium compounds interact to a lesser extent) • **Stop/withhold** multivalent cation-containing product* until antibiotic course complete. • If cation-containing product* **cannot** be stopped/withheld consider alternative antibiotic. • If concomitant administration necessary dose space as far apart as possible and monitor for treatment failure.	Absorption **not** significantly affected by dairy products.	Absorption **not** significantly affected by food.

Tetracyclines	Co-administration with multivalent cation-containing product*(see table 2)	Co-administration with dairy products	Co-administration with food
Doxycycline, lymecycline, minocycline	Potential **90-100%** reduction in antibiotic plasma levels. • **Stop/withhold** multivalent cation-containing product* until antibiotic course complete. • If cation-containing product* **cannot** be stopped/withheld consider alternative antibiotic**.** • If concomitant administration necessary dose space as far apart as possible and monitor for treatment failure. **Note**: doxycycline undergoes enterohepatic recycling which could reduce the effectiveness of dose spacing at preventing treatment failure.	Absorption **not** significantly affected by dairy products.	Absorption **not** significantly affected by food.
Tetracycline, oxytetracycline	Potential **90-100%** reduction in antibiotic plasma levels. • **Stop/withhold** multivalent cation-containing product* until antibiotic course complete. • If cation-containing product* **cannot** be stopped/withheld consider alternative antibiotic**.** • If concomitant administration necessary dose space as far apart as possible and monitor for treatment failure.	**Avoid** concurrent administration with: • milk • yoghurt • calcium fortified orange juice for **2 hours before or after** antibiotic.	**Avoid** concurrent administration with food for **2 hours before or after** antibiotic.

References

1. Electronic Medicines Compendium. [online] Available at: http://www.medicines.org.uk [Accessed 9th May 2023]

2. Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press http://www.medicinescomplete.com [Accessed 9th May 2023]

3. Stockley's Drug Interactions. [online] London: Pharmaceutical Press http://www.medicinescomplete.com [Accessed 9th May 2023]

4. Pitman SK, Hoang UTP, Wi CH, Alsheikh M, Hiner DA, Percival KM. Revisiting Oral Fluoroquinolone and Multivalent Cation Drug-Drug Interactions: Are They Still Relevant? Antibiotics (Basel). 2019 Jul 31;8(3):108. doi: 10.3390/antibiotics8030108. PMID: 31370320; PMCID: PMC6784105.

5. Eljaaly K, Helal A, Almandeel T, Algarni R, Alshehri S. Multivalent cations interactions with fluoroquinolones or tetracyclines: A cross-sectional study. Saudi J Biol Sci. 2021 Dec;28(12):6929-6932. doi: 10.1016/j.sjbs.2021.07.065. Epub 2021 Jul 30. PMID: 34866992; PMCID: PMC8626210.

Document Author: Dr Rachael Rodger (Antimicrobial Pharmacist)

Document Prepared by: NHSGGC Antimicrobial Pharmacist Team and NHSGGC Antimicrobial Management Team

Document Approved by: NHSGGC Antimicrobial Utilisation Committee

Date Approved: May 2023 Review Date: May 2026