# Morbidity and mortality associated with the interaction of miconazole oral gel and warfarin

M. N. Pemberton[1]

## Key points

- Highlights that miconazole oral gel and warfarin can interact to cause derangement of anti-coagulation.
- Suggests the risk of interaction is underappreciated by clinicians.
- Notes that nystatin is not thought to interact with warfarin.

Oral candidiasis is a frequently encountered oral fungal infection which can be treated with systemic and topical antifungal agents. Warfarin is a widely used oral anticoagulant. The interaction of miconazole oral gel and warfarin, causing potentiation of anticoagulant activity, has been documented over many years with evidence of occurrence in multiple settings and is a significant patient safety risk. This dangerous interaction remains underappreciated by dentists, doctors, pharmacists and patients, with resulting significant morbidity and mortality still occurring. This paper reports on recent developments concerning this interaction, and the important patient safety issues involved. In situations where topical treatment for oral candidiasis is indicated, nystatin should be prescribed instead of miconazole oral gel in patients taking warfarin, unless close monitoring and titration of the anticoagulant effect is undertaken.

## Introduction

There are few situations in which the routine prescription of a medicine by a dentist can lead to significant morbidity or death. One preventable event is the precipitation of a significant drug interaction between a medication prescribed by the dentist and another medication the patient is already taking. Systemic medications prescribed by dentists, such as antibiotics and painkillers, may be easier to identify as requiring checking for drug interactions, however, topical agents may be less perceived to have the ability to cause a significant drug interaction. This paper will discuss the interaction of miconazole oral gel and warfarin, an interaction that can contribute to mortality and significant morbidity and represents an important patient safety issue for dentists when prescribing.

Oral candidiasis is a frequently encountered oral fungal disease. The most common causative agent is *Candida albicans* although other species such as *Candida tropicalis, Candida glabrata* and *Candida dubliniensis* are also found.[1,2] Multiple local factors, such as denture wearing and systemic factors, such as diabetes mellitus, predispose to candidal infection. Miconazole is an antifungal agent that has been available for over 40 years to treat fungal infections. Miconazole can act as an antifungal agent by damaging the integrity of the fungal cell membrane, by inhibiting the formation of germ tubes and by altering fungal adherence.[3] It was initially developed as a systemic parenteral agent as it was thought not to be significantly absorbed through the gastrointestinal tract. As a systemic agent it was quickly superseded by fluconazole and itraconazole which allowed predictable high levels of absorption following oral administration, and miconazole was developed as an agent for topical use. For over 30 years miconazole has been marketed as an oral gel (trade name: Daktarin) for the treatment of oral candida infections, as well as preparations for the treatment of candida vaginitis.

Warfarin is a widely used anticoagulant that has been in clinical practice for many years.[4] Its anticoagulant use includes the prevention and treatment of thromboembolic events in patients with venous thromboembolism, prosthetic heart valves and atrial fibrillation.[5,6] Warfarin is metabolised by the hepatic microsomal enzymes of the CYP family. The cytochrome P450 enzyme CYP 2C9 is the main site of metabolism. Its effects are monitored by measurement of the international normalized ratio (INR). Warfarin has a narrow therapeutic index and its anticoagulant effect can be significantly influenced by changes in concomitant medication, diet, alcohol consumption, and other factors.[7] Many warfarin users are elderly with a high frequency of co-morbidity, and a polypharmacy of medication, and multiple predisposing factors for the development of oral candidiasis. In this situation, systemic anti-mycotic therapy is more likely to be contra-indicated due to the potential for drug interactions, with topically applied agents generally thought to offer safer treatment alternatives.

[1]Consultant in Oral Medicine and Honourary Professor, Division of Dentistry, Faculty of Biology, Medicine and Health, University of Manchester; University Dental Hospital of Manchester, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, M15 6FH
Correspondence to: Mike Pemberton
Email: Mike.Pemberton@manchester.ac.uk

Refereed Paper. Accepted 27 April 2018
DOI: 10.1038/sj.bdj.2018.534



Official journal of the British Dental Association.

**Box 1 Case reported December 2012, Republic of Ireland[32]**

A 63-year-old male was on warfarin for atrial fibrillation. He developed soreness in his mouth and his wife attended a local pharmacy on his behalf. She described her husband's symptoms to the pharmacist. Miconazole oral gel was dispensed. The patient used the gel twice daily for five days. He developed a haematoma on the fifth day and pains in his stomach on the seventh. On the eighth day he was admitted to hospital and he died on the sixteenth day after initiating use of the oral gel. It was thought that he died from a spontaneous intra-cerebral haemorrhage.

**Box 2 Case reported December 2014, North West England[33]**

A 73-year-old man living in a nursing home was on long-term warfarin following a stroke. His GP subsequently also prescribed him miconazole. Following a fall from a chair he was admitted to hospital. This combination of drugs and their effect on his blood clotting were initially not recognised. A later blood test showed an INR of 12. The patient was given treatment but he died due to internal bleeding three days after being admitted. At the inquest into his death the coroner was reported as stating that the patient would not have died as a result of the fall if doctors had recognised the problem caused by this particular mixture of drugs.

**Box 3 Case reported March 2016, South Wales[34]**

An 80-year-old female on long-term warfarin developed an oral candida infection and was prescribed miconazole oral gel. Fifteen days after commencing the miconazole she died from a brain haemorrhage after being found unconscious in bed. At the subsequent inquest the assistant coroner said 'The deceased died from an intracranial haemorrhage, the effects of which may have been contributed to by the combined use of warfarin and miconazole gel medications.' He further stated 'I intend to write to several medical bodies including the NHS to highlight the potential dangers'.

## Miconazole oral gel: pharmoacokinetics and peer reviewed reports

Azole antifungal agents, including miconazole, are known to be inhibitors of the cytochrome P450 enzyme system, which is also responsible for the metabolism of warfarin.[8] By this mechanism, miconazole has the potential to inhibit warfarin metabolism and thereby increase the severity of anticoagulation. The ability of miconazole to be absorbed was initially thought to be low, however, significant levels of miconazole have been directly detected in healthy subjects following administration of miconazole oral gel.[9] More recently, significant amounts of miconazole and an increase in INR have been found in a patient's plasma during concomitant treatment with miconazole oral gel and warfarin, thereby confirming its absorption and effect on INR in a patient.[10] Pharmacokinetic modelling has also shown the potential for interaction between miconazole oral gel and warfarin.[11] In addition, the prolonged duration of effect of miconazole oral gel on warfarin metabolism has become apparent. In one study, six patients treated simultaneously with warfarin and miconazole oral gel were monitored following cessation of miconazole oral gel.[12] An increased INR was observed for an average of 15 days indicating that closer monitoring of INR levels may be required for at least two weeks following withdrawal of miconazole in patients taking warfarin.

There is probably more than one reason why this drug interaction is apparent in some patients and not others. It has been estimated that up to 27% of the miconazole is absorbed systemically, however, it is likely that the amount absorbed is increased where there is significant oral mucosal or gastrointestinal inflammation.[11] There may also be a large degree of interpatient variability in the pharmacokinetics and pharmacodynamics of drug metabolism.[8,11] For example the pharmacokinetic parameters of warfarin have been reported to be affected by several factors, including age and genetic polymorphism in CYP 2C9.[11]

In 1982, the first published clinical case of a drug interaction between miconazole gel and warfarin was described, with the dosage of gel prescribed being 250 mg four times daily for two-weeks.[13] In 1987, the first interaction specifically between miconazole oral gel and warfarin was published with the dosage being 5 ml (25 mg/ml) four times daily.[14] In this case the patient was admitted with melaena ten days after commencement of the gel, with his INR having increased from his normal value of 2.5 to 17.9. Since then, multiple cases of interactions between miconazole oral gel and warfarin have been noted following a similar pattern. This interaction has previously been reported in this journal.[15–17] The electronic bibliographic databases, MEDLINE and EMBASE, contain reports of over 60 cases of this interaction.[10,12–29]

## Miconazole oral gel: drug studies and other literature

In addition to individual cases reports and case series published in the peer-reviewed literature, there are also multiple cases reported as part of larger drug studies and significant numbers of cases reported in the 'grey' literature from around the world, accessible by internet search engines. Some of these cases are reported as drug information alerts, some in pharmacy publications and some in commercial publications.

Pharmacy journals have reported case details of the interaction between miconazole oral gel and warfarin over many years.[30,31] News organisations in both the UK and Ireland have also reported cases of patient fatality involving this interaction and three cases are described in Boxes 1, 2, and 3.[32–34] In May 2016, a patient safety notice from the NHS in Wales was released to all general practitioners, dentists, non-medical prescribers, nurses and pharmacists in Wales where miconazole products are prescribed, dispensed, supplied or administered highlighting this interaction in response to the coroners actions following the case described in Box 3.[35] In June 2016, a Drug Safety Update from the Medicines and Healthcare products Regulatory Agency (MHRA) was released in the UK.[36] The purpose of the update was to remind healthcare professionals that miconazole, including the topical gel formulation, can enhance the anticoagulant effect of warfarin and that if miconazole and warfarin are used concurrently then the anticoagulant effect should be carefully monitored. This drug safety update gave further details of an analysis of relevant reports to the MHRA yellow card scheme operational in the UK. This reporting scheme for possible adverse drug reaction has been in operation since 1963. Initially doctors, dentists and pharmacists could submit reports but more recently patients have been able to submit reports as well. The MHRA reported that up to 13 April 2016, they had received 146 Yellow Cards that reported possible drug interaction between miconazole and warfarin with the majority of reports (128, 88%) concerning the oral gel form of miconazole.[36] The MHRA further reported that the most frequently



Official journal of the British Dental Association.

reported events were: Increased INR (111 reports); contusion (21); haematuria (17); and epistaxis (eight). Approximately half of the 146 cases reported an INR increase above ten and in three cases a fatal outcome was reported as a result of a haemorrhagic event. Since then, further reports of this interaction have occurred indicating an on-going need for further dissemination of the risk involved in concurrent prescription (Box 4).[37,38]

**Box 4 Case reported February 2017, South West England[38]**

A man with complex co-morbidities, including atrial fibrillation for which he was taking warfarin, had two chest infections treated with antibiotics followed by development of oral thrush. He was prescribed miconazole oral gel and one week later developed haemoptysis, attended A&E and was found to have an INR of ten. The possible interaction of miconazole oral gel and warfarin did not appear to have been recognised and he was given IM Vitamin K and sent home. He continued to use the miconazole oral gel. Warfarin was subsequently resumed and 3–4 days later he was admitted to hospital with an acute-on-chronic subdural haematoma. The GP notes were reviewed and the possible interaction between miconazole and warfarin was spotted. The report further reads 'The medical team were contacted to let them know – A member of the team was sceptical that this could have been the cause and interestingly the discharge summary makes no mention of this interaction.'

## Miconazole oral gel: availability, dosage and safety update

In the UK and Ireland, miconazole oral gel is available on prescription from doctors and dentists. A 15 g tube can also be sold over the counter in pharmacies without prescription. In the UK it is available at a concentration of 24 mg/ml. Prior to 2013 the advice in the British National Formulary (BNF) and on the Patient Information Leaflet contained within the packaging was to use 5–10 ml in the mouth four times daily in adult patients.[39] In 2013 there was a revision of the text on the Summary of Product Characteristics for miconazole oral gel with the dosage guidance reducing to 2.5 ml four times daily after meals, and the gel to be retained near oral lesions before swallowing in adult patients.[40] This change in text was subsequently mirrored in the advice on dosage in the BNF and the Patient Information Leaflet.[41,42] This reduction in dosage may be expected to reduce the amount of miconazole that will be absorbed and hence the risk of a drug interaction occurring.

In September 2017, a further Drug Safety Update from the Medicines and Healthcare products Regulatory Agency (MHRA) was released in the UK.[43] The purpose of this new update was to give further advice on avoidance of miconazole oral gel interacting with warfarin. The article stated that since the Drug Safety Update of June 2016, the MHRA had received a further 25 Yellow Card reports, bringing the total possible drug interactions with miconazole and warfarin to 175. The advice now states that patients taking warfarin should not use over-the-counter miconazole oral gel. To help re-inforce this advice, the contraindication to using with warfarin will be clearly reflected on the outer carton and on the tube. If miconazole oral gel is prescribed to a patient on warfarin then the prescriber should closely monitor them and advise that if they experience any sign of bleeding then they should stop miconazole oral gel and seek immediate medical attention. To reflect these changes more prominent and explicit warnings and information have been added to the Summary of Product Characteristics and the Patient Information Leaflet.[44,45] These changes in the UK have also been mirrored by similar changes in guidance in the Republic of Ireland.[46]

General medical practitioners frequently use electronic prescribing systems which automatically warn the prescriber of drug interactions when drugs with known serious interactions are being co-prescribed. These safety systems are rarely available in general dental practice. In addition in dental practice there are also potential risks involved in the reliance on patients to fully declare their current medications to any prescribing dentist. Hence these new, more prominent, warnings on the packaging of miconazole oral gel are to be welcomed as an extra patient safety protection in the attempt to reduce the frequency of this serious interaction occurring inadvertently.

## Nystatin and warfarin

Nystatin has been available as a topical antifungal agent for many years. It was understood that there was no significant absorption and that the chance of interaction with warfarin would be low. In 2012, however, a retrospective case study was published which concluded that both miconazole oral gel and nystatin solution appeared to enhance the anticoagulant activity of warfarin equally.[27] Methodological weaknesses have been identified in this study.[47] Since then the potential of an interaction between nystatin and warfarin has been studied further. A literature review and analysis of UK adverse drug reaction surveillance reports has been undertaken and did not find any evidence of a clinically relevant drug interaction between warfarin and nystatin.[48] A cohort cross-over study with the objective of evaluating the potential drug-drug interaction between warfarin and nystatin oral solution did not find any indication of an interaction, whereas it found clear evidence of an interaction between warfarin and miconazole oral gel.[47] In patients taking warfarin, nystatin oral solution appears to be the safest topical drug to treat oral candidiasis. Nystatin is available as a suspension at a concentration of 100,000 units per ml. The recommended dose in adults is 100,000 units four times a day usually for seven days, and continued for 48 hours after lesions have resolved. It is recommended that administration of the dose is divided between both sides of the mouth.[41]

## Conclusion

There is clear evidence that a drug interaction between miconazole oral gel and warfarin occurs and has the potential to cause significant morbidity and mortality. This dangerous interaction remains underappreciated by prescribers, pharmacists and patients and poses a significant on-going risk to patient safety. Ideally, the two drugs should not be administered concurrently. Where miconazole oral gel and warfarin need to be co-prescribed then the anticoagulant effect should be carefully monitored and, if necessary, the dose of warfarin reduced. Nystatin is not thought to have a significant interaction with warfarin and remains the safest antifungal to use when patients are taking this anticoagulant.


1. Kragelund C. Exploiting new knowledge of Candidal infection for future antifungal combat. *Oral Dis* 2017; **23:** 543–547.
2. Singh A, Verma R, Murari A, Agrawal A. Oral Candidiasis: an overview. *J Oral Maxillofac Pathol* 2014; **18:** S81–S85.
3. Isham N, Ghannoum M A. Antifungal activity of miconazole against recent Candida strains. *Mycoses* 2010; **53:** 434–437.
4. Stewart A, Ganguli A, Fitzgerald R, Pirmohamed M. Variation in warfarin prescribing and dosing in the UK: a national survey of anticoagulation clinics. *J Clin Pharm Ther* 2015; **40:** 466–471.
5. Albers G W, Dalen J E, Laupacis A, Manning W J, Petersen P, Singer D E. Antithrombotic therapy in atrial fibrillation. *Chest* 2001; **119(suppl):** 194S206S.
6. Stein P D, Alpert J S, Bussey H I, Dalen J E, Turpie A G G. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. *Chest* 2001; **119(suppl):** 220S227S.

7. Wells P S, Holbrook A M, Crowther N R, Hirsh J. Interactions of warfarin with drugs and food. *Ann Intern Med* 1994; **121:** 676–683.
8. O'Reilly R A, Goulart D A, Kunze K L *et al*. Mechanisms of stereoselective interaction between miconazole and racaemic warfarin in human subjects. *Clin Pharmacol Ther* 1992; **51:** 656–667.
9. Cardot J-M, Chaumont C, Dubray C, Costantini D, Aiache JM. Comparison of the pharmacokinetics of miconazole after administration via a bioadhesive slow release tablet and an oral gel to healthy male and female subjects. *Br J Clin Pharmacol* 2004; **54:** 345–351.
10. Tajima-Okuba R, Tsuruoka S, Moriyama N, Kanneda T, Yamagata K. Interaction of miconazole oral gel with warfarin and cyclosporine in a patient with nephotic syndrome. *CEN Case Rep* 2012; **1:** 55–57.
11. Miki A, Ohtani H, Sawada Y. Warfarin and miconazole oral gel interactions: analysis and therapy recommendations based on clinical data and a pharmacokinetic model. *J Clin Pharm Ther* 2011; **36:** 642–650.
12. Murakami S, Tanaka A, Ido K, Tanaka M. Araki H. Prolonged effects of miconazole oral gel on warfarin anticoagulation even after treatment withdrawal. *Int J Clin Pharmacol Ther* 2016; **54:** 474–476.
13. Watson P G, Lochan B G, Reddind J V. Drug interactions with coumarin derivative anticoagulants. *Br Med J* 1982; **285:** 1045–1046.
14. Colquhoun M C, Daly M, Stewart P, Beeley L. Interaction between warfarin and miconazole oral gel. *Lancet* 1987; **1**: 695–696.
15. Evans J, Orme D S, Sedgwick M L, Youngs G R. Treating oral candidiasis, potentially fatal. *Br Dent J* 1997; **182:** 452.
16. Pemberton M N, Sloan P, Ariyaratnam S, Thakker N S, Thornhill M H. Derangement of warfarin anticoagulation by miconazole oral gel. *Br Dent J* 1998; **184:** 68–69.
17. Pemberton M N, Oliver R J, Theaker E D. Miconazole oral gel and drug interactions. *Br Dent J* 2004; **196:** 529–531.
18. Shenfield G M, Page M. Potentiation of warfarin action by miconazole oral gel. *Aust N Z J Med* 1991; **21:** 928.
19. Pillans P, Woods D J. Interaction between miconazole oral gel (Daktarin) and warfarin. *N Z Med J* 1996; **109:** 346.
20. Ezsias A, Wojnarowska F, Juniper R. Topical use of miconazole antifungal oral gel on warfarinised patients, a word of caution. *Dent Update* 1997; **24:** 421–422.
21. Ariyaratnam S, Thakker N S, Sloan P, Thornhill M H. Potentiation of warfarin anticoagulation activity by miconazole oral gel. *BMJ* 1997; **314:** 349.
22. Marco M, Guy A J. Retroperitoneal haematoma and small bowel intramural haematoma caused by warfarin and miconazole interaction. *Int J Oral Maxillofac Surg* 1998; **27:** 485.
23. Silingardi M, Ghirarduzzi A, Tincani E, Iorio A, Iori I. Miconazole oral gel potentiates warfarin anticoagulant activity. *Thromb Haemost* 2000; **83:** 794–795.
24. Igarashi M, Kuroiwa A, Hayashi M *et al*. Serious interaction between miconazole gel and warfarin. *J Jpn Hosp Pharm* 2000; **26:** 207–211.
25. Ogard C G, Vestergaard H. Interaction between warfarin and oral miconazole gel. *Ugeskr Laeger* 2000; **162:** 5511.
26. Ikejima T, Hirota Y, Okuyama E *et al*. Potentiation of warfarin anticoagulation by miconazole oral gel. *Jpn J Clin Pharmacol Ther* 2002; **33:** 13–16.
27. Kovac M, Mitic G, Kovac Z. Miconazole and nystatin used as topical antifungal drugs interact equally strongly with warfarin. *J Clin Pharm Ther* 2012; **37:** 45–48.
28. Ufondu C C, Ferrins P, Cushen A, Quinn J. Warfarin and topical miconazole: the potential for a clinically significant interaction. *Ir J Med Sci* 2013; **182:** 153–154.
29. De Pauw A, De Backer T. Miconazole buccal gel and risk for systemic bleeding: how certain topical formula can interfere with anticoagulation. *Acta Clin Belg* 2015; **70:** 121–123.
30. Buck D, Miconazole gel and warfarin. *Pharmacy magazine,* 2015. Available at http://www.pharmacymagazine.co.uk/interaction-alert (accessed January 2018).
31. Filmer S. Warfarin and oral miconazole: a major interaction overlooked in practice. *The Pharmaceutical Journal* 2012; **288:** 527–528. Available at https://www.pharmaceutical-journal.com/learning/learning-article/warfarin-and-oral-miconazole-a-major-interaction-overlooked-in-practice/11099329.article?firstPass=false (accessed January 2018).
32. O'Loughlin A. €250k after man bled to death while using gel. Irish Examiner, 2012. Avahttps://www.irishexaminer.com/ireland/520k-after-man-bled-to-death-while-using-gel-217623.html (accessed January 2018).
33. Mail Online. Gardener bled to death after minor fall because drug combination stopped his blood clotting – and doctors ignored the problem until it was too late. *Daily Mail*, 2014. Available at http://www.dailymail.co.uk/news/article-2859125/Gardener-bled-death-minor-fall-drug-combination-stopped-blood-clotting-doctors-ignored-problem-late.html (accessed January 2018).
34. BBC News. Report to prevent future deaths after lollipop lady dies. BBC, 2016. Available at https://www.bbc.co.uk/news/uk-wales-south-west-wales-35711152 (accessed January 2018).
35. NHS Wales Patient Safety Notice. Risk of patient harm from an interaction between miconazole and coumarin anticoagulants. NHS Wales, 2016. Available at http://www.primarycareservices.wales.nhs.uk/sitesplus/documents/1150/PSN032%20May%202016.pdf (accessed January 2018).
36. Medicines and Healthcare products Regulatory Agency Drug Safety Update. *Topical miconazole, including oral gel: reminder of potential for serious interactions with warfarin.* London: Department of Health, 2016. Available at https://www.gov.uk/drug-safety-update/topical-miconazole-including-oral-gel-reminder-of-potential-for-serious-interactions-with-warfarin (accessed January 2018).
37. NHS Greater Glasgow and Clyde Area Drug and Therapeutics Committee. Warfarin and miconazole oral gel potential interaction. *Greater Glasgow and Clyde Medicines.* 2017. Available at http://www.ggcmedicines.org.uk/blog/warfarin-and-miconazole-oral-gel-potential-interac/ (accessed January 2018).
38. NHS England. Update for primary care in the South West: GP Bulletin. 2017. Available at https://www.england.nhs.uk/south/wp-content/uploads/sites/6/2017/02/gp-bulletin-199.pdf (accessed January 2018).
39. British National Formulary 64 (2012). BMA, RPS: London.
40. Summary of Product Characteristics. Daktarin Oral gel. Janssen Pharmaceutica NV: Beerse, Belgium, 2013.
41. British National Formulary 73. BMA, RPS: London, 2017.
42. Patient Information Leaflet. Daktarin 2% Oral Gel. Janssen Pharmaceutica NV: Beerse, Belgium, 2014.
43. Medicines and Healthcare products Regulatory Agency Drug Safety Update. *Miconazole (Daktarin): over-the-counter oral gel contraindicated in patients taking warfarin.* London: Department of Health, 2017. Available at https://www.gov.uk/drug-safety-update/miconazole-daktarin-over-the-counter-oral-gel-contraindicated-in-patients-taking-warfarin?dm_i=EQ,575R3,C9JI9T,JZRIO,1 (accessed January 2018).
44. Summary of Product Characteristics. Daktarin Oral gel. Janssen Pharmaceutica NV: Beerse, Belgium, 2017.
45. Patient Information Leaflet. Daktarin® 2% Oral Gel. Janssen Pharmaceutica NV: Beerse, Belgium, 2017.
46. Therapeutics Today. Safety update on use of miconazole oral gel. National Medicines Information Centre 2018; 1. Available at http://www.stjames.ie/GPsHealthcareProfessionals/Newsletters/TherapeuticsToday/TherapeuticsToday2018/Therapeutics%20Today%20Jan%202018.pdf (accessed January 2018).
47. Hellfritzsch M, Pottegard A, Paedersen A J T *et al.* Topical Antimycotics for Oral Candidiasis in Warfarin Users. *Basic Clin Pharmacol Toxicol* 2017; **120:** 368–372.
48. Pemberton M N. Nystatin and miconazole: pharmacological and clinical evidence regarding interactions with warfarin. *Oral Dis* 2016; **22:** 761–765.




Official journal of the British Dental Association.