RAPID ONSET OF VERY HIGH INR VALUES WHEN ROXITHROMYCIN PRESCRIBED WITH WARFARIN CHALLENGES THE ACCEPTED MECHANISM

Ruth L Savage[1,2], Michael V Tatley[1]

[1]New Zealand Pharmacovigilance Centre, Dunedin School of Medicine, University of Otago, Dunedin;
[2]Department of General Practice, University of Otago, Christchurch, New Zealand.

BACKGROUND

Two recent reports to the New Zealand Centre for Adverse Reactions Monitoring (CARM) described International Normalised Ratios (INRs) of 16.1 and 8.4 on day 3 and 4 after roxithromycin was added to warfarin. In a 2015 Australian study five of 72 anticoagulated elderly patients with INR values >10 had taken roxithromycin with warfarin.[1]

No effects on major pathways of warfarin metabolism by roxithromycin have been found. [2] CYP3A4 inhibition has been the proposed mechanism but this is a minor pathway and inhibition by roxithromycin is weak.[2] It is suggested that the clinical significance of the interaction may be increased by severe illness, polypharmacy, renal dysfunction and increased warfarin sensitivity.[1,3,4]

We present an evaluation of the 30 case reports of this interaction submitted to CARM between 1992 and 2015.

OBJECTIVE

To investigate the potentiating effect of roxithromycin on warfarin in reports to CARM.

METHOD

1. Report review for patient characteristics.
2. Analysis of reporting frequency of roxithromycin and other macrolide/warfarin interactions and other CYP3A4 dependent interactions with macrolides. Comparison with Australian data.[5]

RESULTS

The indications for roxithromycin were upper or lower respiratory tract infection.

Table 1 shows the INR range and mean after roxithromycin was added to warfarin. *Figure 1* shows the INR values by day of roxithromycin treatment and *Figure 2* the age and gender distribution.

INR values for eight patients measured on day 3 of roxithromycin treatment were 4.3 to 16.7, median 8.8, mean 10.4.

Twelve patients experienced haemorrhage, four serious.

Table 1 indicates that:

- Most patients were taking long term warfarin and had therapeutic INRs prior to roxithromycin indicating stable anticoagulation.
- Polypharmacy[7] increased markedly around the start of roxithromycin.
- Nine patients recently commenced medicines also known to interact with warfarin. Five more started other antibiotics that interact rarely.[8]
- Twelve patients were hospitalised and/or had pneumonia (serious infection).
- The mean daily dose of warfarin was moderate to low based on doses required by warfarin sensitive patients.[6] Mean daily doses in patients aged >75 cf <75 yrs were 3.2 v 5.2 mg.

Table 2 shows a similar pattern of reporting of macrolide interactions in Australia and New Zealand.

Figure1: INR Value by day after Roxithromycin added to Warfarin

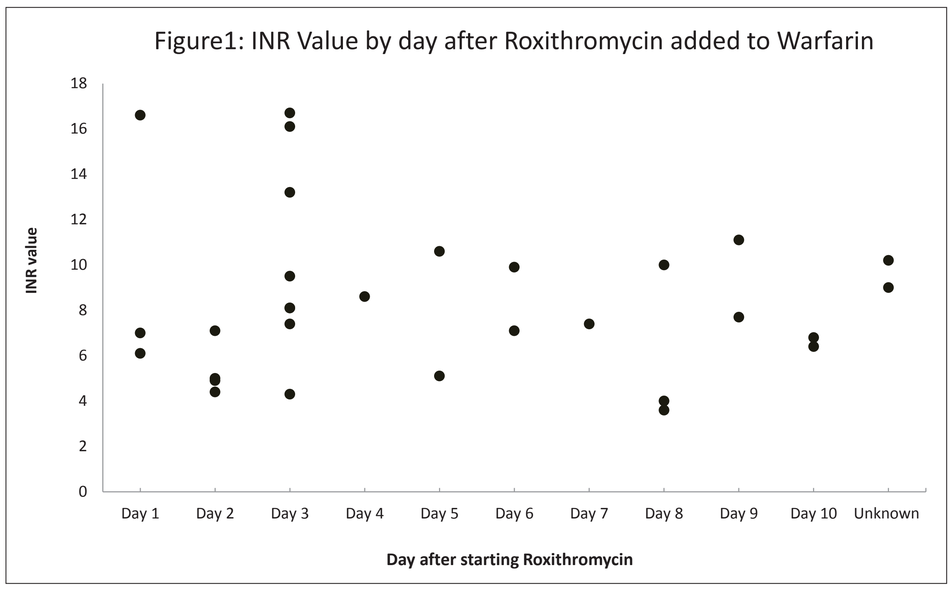


Table 1: Features of case reports of a roxithromycin/warfarin interaction in the New Zealand Pharmacovigilance Centre database (n=30 reports)

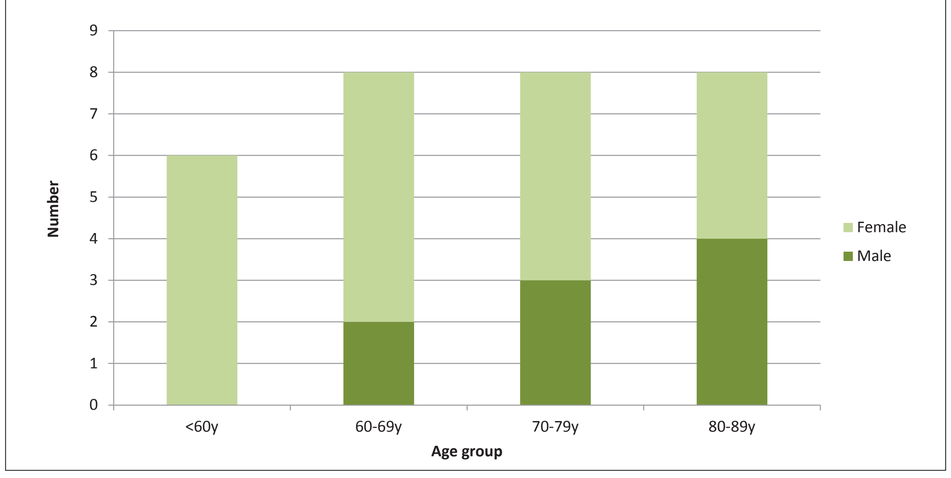
Gender M:F	Age yrs (mean)	INR (mean)	Roxithromycin duration days to INR (mean)	Pre-roxithromycin INR (mean)	Bleeding episodes (%)	Serious Infection (%)	Other potentially contributing acute conditions (%)	Potentially interacting medicines in short term (%)	Warfarin daily dose, mg (mean)	Warfarin longterm** (%)	Poly-pharmacy at INR increase*** (% patients)	Polypharmacy long term (% patients)
9:21	23 - 88 (66.8)	3.6 - 16.7 (7.6)	1 - 10 (4.6) Unknown = 2	2.0 - 3.7 (2.5) Usually stable = 1 Unknown = 9	12/30* (40.0)	12/22 (54.5)	3/30 (10.0)	14/30 (46.7)	1.5 - 13.0 (4.4) Unknown = 2	19/24 (79.2)	25/30 (83.3)	11/30 (36.7)

* Denominators are the number of patients with the reported information;
** Warfarin treatment considered long term when the duration was reported as long term or, where duration specified, at least two months;
*** Polypharmacy defined as 5 or more medicines.[7]

Table 2: Interactions with Macrolides in reports to CARM and ADRAC[3]

Drug	Interacting drug	No of interaction reports CARM 1992 - 2015	No of interaction reports ADRAC 1995 - 2004	Total reports for macrolides CARM	Total reports for macrolides ADRAC
Warfarin	Roxithromycin	30	53	270	737
	Clarithromycin	0	7	53	193
	Erythromycin	4	6	777	597
	Azithromycin	0	4	43	111
Anticonvulsants	Roxithromycin	0	5	270	737
	Erythromycin	4	3	777	597
	Clarithromycin	0	2	53	193
Statins	Roxithromycin	3	5	270	737
	Erythromycin	14	4	777	597
	Clarithromycin	0	2	53	193

Figure2: Age/Gender distribution



DISCUSSION

CARM data supports the Australian evidence that a role for CYP3A4 is unlikely given the high proportion of roxithromycin/warfarin interaction reports compared with other macrolides and other roxithromycin CYP3A4 mediated reactions (Table2).[5]

The report analysis suggests increased clinical significance of a roxithromycin/warfarin interaction through acute anticoagulation destabilisation with severe infection and other interacting medicines, and increased warfarin sensitivity influenced by older age.

Roxithromycin is marketed in New Zealand, Australia and parts of Europe and Asia. There is no consistent caution against its use with warfarin.

New Zealand's Medsafe advises INR measurement on day three of macrolide antibiotics in keeping with Stockley's Interaction Alerts.[4,8] The CARM reports suggest this has reduced the risk of haemorrhage with roxithromycin. Advice in product information is less specific.[9,10,11] However, by day 3 some patients already have a significant increase in INR suggesting that earlier monitoring of INR in vulnerable patients may be advisable.

In the 2017 New Zealand antibiotic guideline for respiratory infection[12] macrolides are first choice antibiotics only for atypical pneumonia, pertussis and, if penicillin allergy, other pneumonias and group A haemolytic streptococcal pharyngitis.

We suggest limiting roxithromycin in patients taking warfarin to infections for which macrolides are first choice in accordance with local guidelines.

CONCLUSION

Serious infection and acute polypharmacy are the strongest predictors of a clinically important interaction between roxithromycin and warfarin in this study.

The INR increase may be rapid and severe.

The findings reinforce the low likelihood of the historically prevailing opinion that the interaction is CYP3A4 mediated.

The findings support INR measurement within three days when roxithromycin is added to warfarin.

Roxithromycin should be avoided in patients taking warfarin where a macrolide is not the most effective option.

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