Possible Interaction of Roxithromycin with Warfarin
Updated Review of ADR Reports

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Summary

Roxithromycin is an ether oxime derivative of erythromycin, but is reported to have a less inhibiting effect on the cytochrome P450 system than the latter compound. Unlike erythromycin, it is considered to be devoid of any clinically significant interactions with oral anticoagulants. The Centre for Adverse Reactions Monitoring (CARM) of New Zealand and the Adverse Drug Reactions Advisory Committee (ADRAC) of Australia are responsible for monitoring adverse reactions to drugs for their countries. They received 7 (CARM) and 9 (ADRAC) reports of possible interactions of roxithromycin with warfarin during the period 1992-1995. Roxithromycin appears to have a potentiating effect on warfarin, although considerably less so than erythromycin. This is likely to be particularly clinically significant in patients receiving polypharmacy and in elderly or compromised patients.

Roxithromycin, a semisynthetic second generation macrolide antibiotic, is an ether oxime derivative of erythromycin. However, its absorption is more rapid and less variable than erythromycin, and it has a longer half-life than the parent compound. It is, therefore, a drug of preference for many Gram-positive infections, particularly in nonhospitalised patients.

Macrolide antibiotics are known to inhibit cytochrome P450 enzymes, but animal pharmacological studies indicate that roxithromycin has a weaker inhibiting effect on this enzyme system than erythromycin. These enzymes are responsible for the degradation and clearance of many commonly prescribed drugs, such as carbamazepine, theophylline and warfarin.

Erythromycin is known to prolong the half-life of some anticonvulsants and oral anticoagulants, and often potentiates their effects. Roxithromycin, therefore, is predicted to have no interaction with drugs that are metabolised by the hepatic microsomal P450 system. Indeed, no significant interactions of roxithromycin with carbamazepine in healthy volunteers and with theophylline in both healthy volunteers and patients with chronic obstructive airways disease were observed. Similarly, no interaction between roxithromycin and warfarin was found in a group of healthy volunteers. The manufacturer’s data sheet worldwide, therefore, makes no comment on the effect of concomitant administration of roxithromycin and oral anticoagulants.

The Centre for Adverse Reactions Monitoring (CARM) and the Adverse Drug Reactions Advi-
sory Committee (ADRAC) are responsible for monitoring all medicine-related adverse effects for the Ministry of Health of New Zealand and the Therapeutics Goods Administration of Australia, respectively. The CARM has been receiving spontaneous reports of adverse reactions from the prescribers since 1965, and maintains a database for follow-up studies; similarly, the ADRAC has been collecting spontaneous reports since 1964, although computerisation of its database was established only in November 1972.

Roxithromycin has been available in both New Zealand and Australia on prescription since 1992. The CARM received 3 reports of suspected interactions of roxithromycin with warfarin during the period 1992-1993. The ADRAC also received 4 similar cases in the same period. This paper presents an updated review of the reports of possible interactions of roxithromycin with warfarin received by these 2 centres, and their clinical implications.

Methods

New Zealand and Australia, like other industrialised countries, employ a voluntary (spontaneous) reporting system for monitoring adverse drug reactions (ADR). They utilise a comparable system of data collection and analysis, and are members of the WHO Collaborating Programme for International Drug Monitoring. Both countries have actively encouraged clinicians (prescribers) and pharmacists to report to them, and use a specially designed card for reporting (H1574 in New Zealand and the ‘blue card’ in Australia). The cards are assessed by a clinical pharmacologist or clinician for interpretations and their causal relationship.

Causality is assessed according to the guidance provided by the WHO Collaborative Centre for Adverse Drug Reaction monitoring. The WHO classifies causality on 4 levels, numbered 1 to 4 in decreasing order of confidence, and on 2 levels for incompleteness. A reaction categorised as ‘certain’ (= 1) indicates a clinical event and/or a laboratory test abnormality that occurs in a plausible time in relation to drug administration and that is unlikely to be due to a concurrent disease or other drugs or chemicals. In this situation, response to dechallenge of the drug should be clinically plausible and the reaction should recur after rechallenge. An ADR where no rechallenge is performed but the reaction improved after dechallenge is usually classified as ‘probable’ (= 2). A ‘possible’ (= 3) reaction indicates an association between an ADR and the causative agent, but information regarding dechallenge or rechallenge is not available. Lack of any clinical or pharmacological evidence of an association is categorised as ‘unlikely’ (= 4). Unclassified (= 5) and unclassifiable (= 6) indicate, respectively, that additional data are required to make a decision and further data cannot be obtained.

It is, therefore, often necessary to obtain further information from the notifier and/or the manufacturer. All relevant information is stored on an in-house local network or mainframe-based database. Original notification cards and related correspondence are also kept at the CARM and ADRAC for future reference.

At both centres, computer printouts of all ADR reports in relation to roxithromycin during the period May 1992-April 1995 were obtained for further analysis. All original reports relating to a possible interaction between roxithromycin and warfarin were scrutinised. All patients received the usual recommended dose of roxithromycin, namely 300mg daily.

Data Analysis

As the number of reports received was small, no formal statistical analysis was required.

Results

Data at CARM

The CARM received 86 reports of possible adverse reactions in relation to roxithromycin since its introduction to the New Zealand market in 1992. Figures 1 and 2 illustrate an analysis of system class of all spontaneous reactions in these