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CASE REPORT

Pharmacokinetic interaction between taxanes and amiodarone leading to severe toxicity

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Keywords amiodarone, docetaxel, mucositis, paclitaxel, pharmacokinetics, skin reaction

ADVERSE EVENT

A drug interaction leading to severe skin and mucosal toxicity.

DRUGS IMPLICATED

Paclitaxel, docetaxel and amiodarone.

THE PATIENT

A 77-year-old woman with a history of hypertension, hyperlipidemia, and palpitations, managed with amiodarone, was treated for HER2-positive invasive ductal breast cancer with paclitaxel and trastuzumab as an adjunct to surgery.

EVIDENCE THAT LINKS THE DRUG TO THE EVENT

There was a strong temporal relationship between the taxane therapy and the development of severe skin and mucosal toxicity due to an unexpected reduction in taxane clearance.

MANAGEMENT

Initially, conversion of paclitaxel to docetaxel, then cessation of docetaxel, symptomatic treatment, rehydration and placement of a nasogastric tube.

MECHANISM

Increased exposure to paclitaxel and subsequently docetaxel due to interaction with amiodarone was suspected and confirmed on pharmacokinetic sampling. Analysis of two blood samples taken 9 and 10 days after docetaxel revealed plasma levels of 4.73 and 4.09 ng ml^{-1}, respectively, leading to a 79% decreased individual (Bayesian maximum *a posteriori*) clearance estimate of 9.15 l h^{-1}, corresponding to an estimated fivefold increase in AUC. Paclitaxel was also present in these samples (20 and 21 days after the last administration).

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IMPLICATIONS FOR THERAPY

Amiodarone inhibits cytochrome P_{450} (CYP) isoforms 2C8 and 3A4 as well as P-glycoprotein (P-gp) for which taxanes are substrates. However, interactions with amiodarone are not specified in the prescribing information. Clinicians should be aware of this interaction, particularly in an ageing population, where more patients requiring taxanes may already be receiving amiodarone for a comorbid cardiac condition.

Tables of Links

TARGETS
Enzymes [2]
CYP3A4
CYP2C8
Transporters [3]
P-gp

LIGANDS
Amiodarone
Docetaxel
Paclitaxel

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

We describe a case of a life-threatening drug–drug interaction in a patient receiving long-term amiodarone who was newly initiated on taxane chemotherapy (paclitaxel and then docetaxel). The patient developed severe skin exfoliation and mucositis leading to diarrhoea, odynophagia and subsequent dehydration requiring hospitalization. There are no similar previous reports in the literature. Pharmacokinetic analysis confirmed reduced clearance of paclitaxel and docetaxel. The purpose of this report is to alert clinicians to the potential problems of combining taxanes with amiodarone.

A 77-year-old woman (53 kg, 147 cm) with a history of hypertension, hyperlipidaemia and palpitations (not further specified) was treated for HER2-positive invasive ductal breast cancer (TNM stage cT1–2 cN1) with weekly paclitaxel (80 mg m^{-2}) and trastuzumab as an adjunct to surgery. Additional medication included amiodarone, aspirin, atorvastatin, ramipril and torasemide. During the first four cycles of outpatient chemotherapy, she developed increasing abdominal discomfort and skin lesions, starting with a facial rash that progressed to overt peeling of her palms (Figure 1)

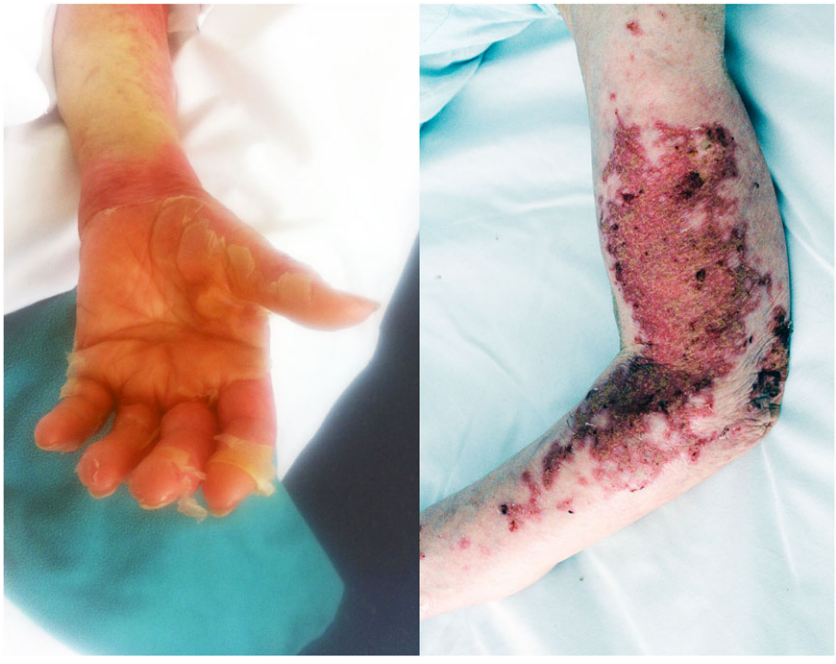

Figure 1

Left hand on day of admission and left arm after 10 days of symptomatic treatment

and soles. The backs of her arms and hands were also involved. She denied excessive sun-exposure. A diagnosis of a rare paclitaxel-induced skin reaction was made. Treatment was switched from paclitaxel to reduced-dose docetaxel (100 mg or 75 mg m^{-2} weekly) because of paclitaxel's known potential for skin toxicity. Three days after the first administration of docetaxel, she developed pain on swallowing, diarrhoea and vomiting; mucositis was diagnosed. Five days later she was admitted to hospital for rehydration, antiemetic therapy and analgesia for increasingly painful exanthemata of her arms and legs. Chemotherapy was discontinued and intravenous hydration was initiated alongside local and systemic symptomatic treatment of the skin reactions with prednisone, ointments and cooling (Figure 1). A nasogastric tube was placed for enteral feeding and administration of oral medicines. Leucocyte counts one month before, during and 9 days after paclitaxel treatment were 7.90, 4.88 and 10.91 $\times 10^9$ l^{-1} (normal range 3.5–10 $\times 10^9$ l^{-1}) respectively.

Analysis of two blood samples taken 9 and 10 days after docetaxel revealed plasma levels of 4.73 and 4.09 ng ml^{-1}, respectively. Bayesian maximum *a posteriori* estimates and confidence intervals for her pharmacokinetic parameters were derived from a previously published population pharmacokinetic model in patients not treated with CYP-enzyme inhibitors [4] using NONMEM version 7.3.0. (ICON Plc, Dublin, Ireland). The estimated individual clearance (CLi) was 9.15 l h^{-1} (95% CI: 9.06–9.26 l h^{-1}), which was 79% lower than the typical clearance of the simulated study (44.1 l/h^{-1}, 95% CI: 38.9–49.2 l h^{-1}). The corresponding $AUC_{0-\infty}$ (75 mg m^{-2}) estimated as dose/CLi was 10.9 mg l h^{-1} (95% CI: 10.80–11.04 mg/l h^{-1}) compared to 2.27 mg l h^{-1}, therefore indicating an approximate fivefold increase. The patient's central volume of distribution was 9.03 l (95% CI: 4.4–18.5 l), which was similar to the typical central volume of distribution of 9.8 l [4]. One thousand Monte Carlo simulations indicated that the two measured docetaxel concentrations in the patient presented here were largely above the 97.5th percentile of the expected normal exposure range (see Supporting Information Figure S1) [4]. Paclitaxel was also present in these samples (20 and 21 days after the last administration, respectively), but concentrations were below the validated lower limit of quantification (<0.5 ng ml^{-1}) [5]. Under normal conditions, paclitaxel should not be detectable 11 days after the last administration.

The patient was discharged two weeks later with near resolution of the skin and mucosal lesions. Chemotherapy was continued with trastuzumab but without a taxane. There were no recurrences of dermatological or gastrointestinal toxicity on follow-up. She gave full written informed consent for anonymous publication of her health-related data. The case was reported to the pharmacovigilance unit of the national authority for therapeutic products (Swissmedic).

Paclitaxel and docetaxel are taxanes used in chemotherapy of certain solid tumours (including breast cancer). They exert their effects by interfering with microtubule breakdown during mitosis. Both are substrates of the efflux pump P-glycoprotein (P-gp) which eliminates them from cells. Paclitaxel is inactivated by cytochrome P_{450} (CYP)2C8 (major pathway) and CYP3A4 (minor pathway), whereas docetaxel is mostly inactivated by CYP3A4 [6]. Skin reactions to taxanes, although rare, are dose-dependent [7].

Amiodarone, an antiarrhythmic drug, is a strong P-gp inhibitor [8] and a moderate CYP3A4 inhibitor. There is evidence for an additional inhibitory effect on CYP2C8 [9]. While one case of docetaxel overdose due to pharmacokinetic interaction with dronedarone (like amiodarone a P-gp and CYP3A4 inhibitor) has been described previously [10], the present case is the first description of an amiodarone–taxane interaction resulting in a significant reduction in taxane clearance. Four cases of mucositis occurring after co-administration of docetaxel and amiodarone are listed in the World Health Organization's VigiBase® global individual case safety report (ICSR) database, the world's largest ICSR repository [11]. We also postulate a pharmacodynamic interaction between amiodarone and taxanes because amiodarone causes a variety of skin reactions [12].

This case has important implications. Firstly, drug–drug interactions between chemotherapeutic agents and long-term medication can lead to life-threatening and costly consequences. Secondly, it shows the influence of amiodarone on taxane metabolism, a combination that will increase as more patients with cardiac comorbidities are treated in an oncological setting. Thirdly, due to amiodarone's 20–100 day half-life [13], its effect on taxane metabolism remains well beyond its discontinuation. It may be advisable to consider alternative cytostatic agents for patients receiving, or who have recently received, amiodarone. We also suggest caution when combining other CYP2C8 inhibitors with paclitaxel.

Competing Interests

No authors received support from any organization for the submitted work or had financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years or other relationships or activities that could appear to have influenced the submitted work. This research received no specific funding.

Accompanying statement

Data obtained from the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden are reported in the discussion of this case. The information comes from a variety of different sources and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. The information does not represent the opinion of the World Health Organization.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13155/suppinfo

Figure S1 Comparison of expected normal range of docetaxel exposure (grey shaded area indicates the 95% prediction interval) with the patient's docetaxel concentration measurements (red dots) as well as an individual model-predicted exposure profile (red line; dotted lines indicate 95% individual prediction interval calculated as individual prediction ± 1.96 × residual intra-individual error)