Erlotinib and pantoprazole: a relevant interaction or not?

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AIMS

There is increasing evidence that erlotinib exposure correlates well with treatment outcome. In this report we present a case of therapeutic drug monitoring of erlotinib in a patient with a gastric ulcer, treated with the proton pump inhibitor pantoprazole. This agent may cause an unwanted, but not always unavoidable, interaction since absorption of erlotinib is pH dependent.

METHODS

Erlotinib trough concentrations were monitored in a patient during treatment with orally and intravenously administered pantoprazole.

RESULTS

Erlotinib trough concentrations were diminished during high dose intravenously administered pantoprazole, but returned to normal when the dose was reduced and pantoprazole was administered orally.

CONCLUSIONS

More studies are needed to assess the dose dependency of the interaction between pantoprazole and erlotinib. Furthermore, we advise to monitor closely erlotinib plasma concentrations and adjust the erlotinib dose accordingly when a clinically relevant interaction is suspected and no proper dosing guidelines are available.

Introduction

Erlotinib (Tarceva®) is an epidermal growth factor tyrosine kinase inhibitor approved as monotherapy for the treatment of non-small cell lung cancer [1]. Erlotinib may be subject to several pharmacokinetic drug–drug interactions. The drug is metabolized in the liver, mainly by the cytochrome P450 (CYP) isoenzymes 3A4 and, to a lesser extent, by the 1A2 isoenzymes. Inhibition or induction of these isoenzymes may therefore alter systemic erlotinib exposure. For example, inhibition of CYP3A4 by ketoconazole may increase erlotinib exposure by 86% or induction of CYP1A2 by smoking may decrease systemic exposure up to 64% [1, 2]. Furthermore, erlotinib shows a limited solubility at a pH above its pKa of 5.4 and may therefore be prone to malabsorption when co-administered with agents that influence gastric pH [1]. There is increasing evidence that erlotinib exposure correlates with treatment outcome. At steady-state erlotinib plasma trough concentrations are approximately $1.2 \pm 0.5 \text{ mg l}^{-1}$ [3]. In phase I

studies the minimal trough concentration required for adequate tyrosine kinase inhibition was determined to be 0.5 mg l^{-1} [3]. Furthermore, high concentrations have been correlated with an increased risk for development of rash [4, 5]. A cut-off value for development of toxicity has not been determined, but may be similar to therapeutic concentrations since erlotinib is dosed at its maximum tolerated dose (MTD), indicating a small therapeutic window [6]. Besides rash, a side effect of erlotinib can be gastric ulceration, making treatment with antacids or acid secretion inhibitors necessary [1]. In this report we present a case of therapeutic drug monitoring of erlotinib in a patient with a gastric ulcer, treated with the proton pump inhibitor (PPI) pantoprazole.

Case report

A 46-year-old Caucasian woman was initially admitted to our hospital for orthopaedic surgery of a collum fracture.

Figure 1

Erlotinib trough concentrations vs. time after treatment initiation. Grey area expected trough concentrations, --- minimal trough concentrations for effective tyrosine kinase inhibition

However, at the hospital she was also diagnosed with stage 4 non-small cell lung cancer, with bone, left adrenal gland and pancreas metastases. Therefore, erlotinib (dosed 150 mg once daily) was started as palliative treatment. Erlotinib was ingested with a light breakfast. Other drugs that were concomitantly administered during the course of treatment were clindamycin, nadroparin, bumetanide, spironolactone, oxazepam, temazepam, paracetamol, promethazine, nystatin, morphine, flucloxacillin and a macrogol laxative, none of which was thought to influence the pharmacokinetics of erlotinib. One day after the erlotinib treatment was initiated, the patient reported a retrosternal burning sensation. Gastro-intestinal complaints were suspected and since simultaneous administration of antacids would possibly diminish erlotinib absorption, treatment with algeldrate/magnesiumhydroxide (800/400 mg four times daily) was started with intake at least 4 h before or 2 h after intake of erlotinib. Unfortunately, the patient developed a massive gastric bleed as a result of a gastric ulcer. Therefore, despite the unwanted interaction, treatment with antacids was replaced with high dose pantoprazole treatment by continuous infusion (8 mg h⁻¹). After 2 days there were no more signs of bleeding and pantoprazole was switched to 40 mg twice daily by oral administration. Since the combination of a PPI with erlotinib is preferably avoided and no dosing guidelines were available for this combination, plasma concentrations of erlotinib were monitored while continuing the recommended erlotinib dose. Trough concentrations were measured on 2 days before initiation of pantoprazole while on algeldrate/

magnesiumhydroxide therapy, 2 days during continuous intravenous administration of pantoprazole and on 2 days while on oral pantoprazole with a validated assay as described previously, with slight adaptations for the determination of erlotinib [7]. The lower and upper limits of quantitation of the assay were 0.01 and 10 mg l⁻¹, respectively. Accuracy and precision, as determined with internal quality controls during the same analytical run, were within 85–115% and less than 15%, respectively, across the validated concentration range. No ethics committee approval was considered necessary, because erlotinib concentrations were monitored to support routine clinical care and because concentrations were determined from blood that was already drawn for routine clinical chemistry. Results are depicted in Figure 1 where trough concentrations are plotted against days since start of erlotinib therapy. The grey area depicts the expected trough concentration range (1.2 ± 0.5 mg l⁻¹) and the dotted line depicts the minimal required trough concentration for effective tyrosine kinase inhibition of 0.5 mg l⁻¹, as proposed by Hidalgo *et al.* [3]. In short, before initiation of pantoprazole with co-administration of algeldrate/magnesiumhydroxide, plasma concentrations were therapeutic and in the expected concentration range (0.96 and 0.97 mg l⁻¹). During treatment with pantoprazole by continuous infusion, erlotinib concentrations decreased drastically to low and subtherapeutic ranges (0.41 and 0.52 mg l⁻¹), but after switching to oral administration in a lower dose the plasma concentrations returned to normal values (0.87 and 0.96 mg l⁻¹).

Discussion

In this patient erlotinib concentrations were within the normal range before initiation of PPI treatment. The development of the gastric ulcer as a result of high plasma concentrations therefore does not seem likely and may also have been a result of other causes like the use of the low molecular weight heparin nadroparin. During treatment with algeldrate and magnesiumhydroxide, erlotinib concentrations were within the therapeutic range and thus there was no clinically relevant interaction observed between erlotinib and algeldrate/magnesiumhydroxide. When administered in combination with high dose intravenous pantoprazole, plasma concentrations decreased significantly, but, surprisingly, returned to normal after switching to oral administration at a lower dose. Therefore, a clinically relevant interaction was observed during high dose intravenous pantoprazole treatment, but was absent during oral treatment with a lower dose. Previously, in a pharmacodynamic study of pantoprazole, it was shown that mean gastric acid secretion decreased by 83% after a single 40 mg i.v. pantoprazole dose, but was completely inhibited after a 80 mg i.v. dose [8]. We therefore postulate that in our case acid secretion was completely inhibited during continuous pantoprazole infusion of 8 mg h⁻¹ and that there was still remaining acid secretion while on 40 mg pantoprazole administered orally twice daily. It should be taken into account that the oral bioavailability of pantoprazole is 77% resulting in even less exposure and less inhibition of acid secretion when administered by the oral route [9]. This may have resulted in impaired erlotinib solubility and absorption during continuous infusion of high dose pantoprazole, but adequate solubility and absorption during oral treatment of pantoprazole at a lower dose. It should not be ruled out that differences in absorption may also have been partly a result of reduced erlotinib absorption as a result of varying food intake. Furthermore, it is known that pantoprazole is an inhibitor of the ATP-binding cassette transporters ABCB1 and ABCG2 and that erlotinib is a substrate for these transporters [10–12]. Inhibition of these transporters by pantoprazole may therefore also have played a role in obtaining adequate erlotinib exposure despite a limited gastro-intestinal solubility and the role of pantoprazole in inhibition of erlotinib transport by multidrug transporters warrants further investigation. Furthermore, in routine clinical practice a large number of patients already use agents that influence the gastric pH or develop gastric complaints. Although the extrapolation of our findings in a single patient to other cases may be limited, they indicate that more studies should be performed to assess proper dosing guidelines of erlotinib in combination with pantoprazole or other PPIs in different doses and routes of administration. Furthermore, because there is possibly a small therapeutic window for systemic erlotinib exposure,

we advise to monitor closely erlotinib plasma concentrations and adjust the erlotinib dose accordingly when a clinically relevant interaction is suspected and no proper dosing guidelines are available.

Competing interests

There are no competing interests to declare.

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