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Increased INR after gefitinib and acenocoumarol co-administration

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Abstract. – INTRODUCTION: Drug interactions can cause many clinical problems, particularly when the drugs are administered in combination with anticancer agents.

CASE REPORT: A patient required two hospitalizations due to risk of bleeding with altered INR probably due to an interaction between gefitinib and acenocoumarol, which resulted in the potentiation of the effect of the latter and acenocoumarol dose adjustment was needed. A causality assessment between the drug-drug interaction and the augmented INR was conducted according to Naranjo algorithm and was classified as a definite adverse drug reaction.

CONCLUSIONS: Patient's management recommended is to closely monitor for changes in the effects of coumarin derivatives, if administered concomitantly with antineoplasic agents.

Key Words:
Cancer, Coumarin, Drug interaction, Gefitinib.

Introduction

Lung cancer is the leading cause of death in most developed countries. Approximately 80% of lung cancers are non-small-cell lung carcinoma (NSCLC). NSCLC are relatively insensitive to chemotherapy. When possible, they are primarily treated by surgical resection, although chemotherapy is increasingly being used both pre-operatively (neoadjuvant chemotherapy), post-operatively (adjuvant chemotherapy) and as palliative care. A wide variety of chemotherapies are used in advanced (metastatic) NSCLC[1-3]. Gefitinib is an orally active, selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that was found to exhibit antitumor activity *in vitro* and *in vivo* and has shown excellent activity in patients with NSCLC EGFR positive[4].

Acenocoumarol, a vitamin K antagonist and coumarin derivate, is the treatment of choice for long-term oral anticoagulation for prevention and treatment of thromboembolic events. Sensitivity to anticoagulants varies according to the individual and may also vary throughout the course of treatment. Therefore, it is essential to check the International Normalised Ratio (INR) and to adjust patient dosage adequately. Depending on clinical situation and anticoagulation intensity, the optimal therapeutic margin is between INR values of 2.0 and 3.5. Nevertheless, different circumstances may alter these values, such as clinical situation or interactions of acenocoumarol with other drugs[5]. However, there are few reports describing the interaction between anticancer agents and acenocoumarol[6-8].

We report a case of a patient who required two hospitalizations due to risk of bleeding with altered INR probably due to an interaction between gefitinib and acenocumarol, which resulted in the potentiation of the effect of the latter.

Case Report

A 65-year-old male patient from China was admitted to the hospital in March 2013 with an INR of 8.98. Medical records included: hypertension, dyslipidemia, and ex smoker for 9 months. In March 2012, the patient was diagnosed with double mitral lesion with moderate stenosis and double aortic lesion resulting in atrial fibrillation and heart failure. Since then, treatment with acenocoumarol was prescribed and the patient has been stable with functional class I-II/IV of the New York Heart Association (NYHA) and weekly INR values around 2.

In August 2012, the patient was diagnosed with non small cell pulmonary adenocarcinoma with extensive mediastinal bilateral nodal affectation and positive EGFR. Treatment with gefitinib, 250 mg a day, was commenced end of January 2013. He was also receiving omeprazole, rosuvastatin, furosemide, lisinopril, bisoprolol, acenocoumarol 1mg and inhaled formoterol and budesonide. Initially, treatment was well tolerated and there were no adverse events.

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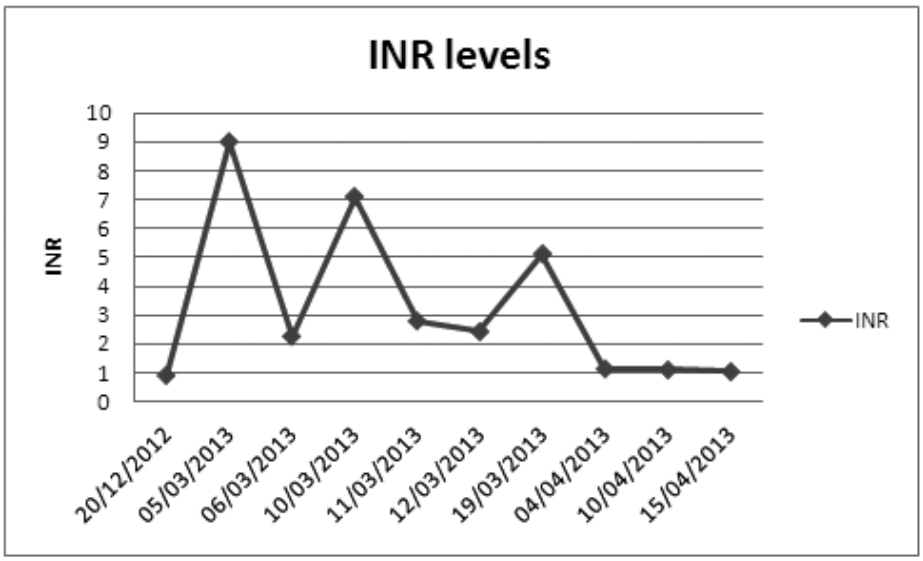

Figure 1. INR monitoring.

On 4th March 2013, the patient visited his GP for routine check on INR with a result of 8.38, no signs of active bleeding. The patient began to feel unwell, fever, shivering and profuse sweating. He was taken to hospital emergency service and treated for severe hypotension. Then he was hospitalized, conscious and orientated with the diagnosis of respiratory sepsis and acenocoumarol overdose. During hospitalization the patient remained stable and urgent acute pathology was ruled out, so acenocoumarol 0.25 mg was re-prescribed on days 5, 6 and 7 of March and 0.5 mg the 8 and 9 March. On 10th March, INR had increased again to 7.09; so, acenocoumarol and gefitinib were suspended due to the possibility of interaction as the latest drug prescribed to the patient was the antineoplasic agent. On 11th and 12th, INR was 2.70 and 2.40, respectively; the patient was discharged with prescription of acenocoumarol 0.5 mg and to resume gefitinib on the 18th. On the 14th and 16th of March, INR was within range; however, the 19th, the patient was rehospitalized with INR of 5.11 and no acute pathology. Acenocoumarol dose was reduced to 0.25 mg and the patient was stable and INR on range. There on, INR has been on range.

A causality assessment between the drug-drug interaction and the augmented INR was conducted according to Naranjo algorithm[9]. The score obtained was 9; therefore, the interaction was classified as a definite adverse drug reaction (ADR). Finally, the ADR was reported to the Pharmacovigilance Centre.

Discussion

Adverse drug reactions (ADR) are considered amongst the leading causes of morbidity and mortality. They are defined by Karch and Lasagna and the World Health Organization as any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy excluding failure to accomplish the intended purpose[10,11]. The case described can be classified as ADR, a pharmacological reaction representing an augmentation of the known pharmacological actions of acenocoumarol. The ADR had a moderate severity as this caused hospitalization. With regard to the casualty of the effect of an interaction, the most commonly used method to determine the likelihood of whether an adverse drug reaction is actually due to the drug rather than the result of other factors is the Naranjo algorithm. The probability is assigned via a score termed definite, probable, possible or doubtful. The interaction described was a "definite ADR" defined by Naranjo et al[9].

On the one hand, patients with lung cancer are relatively advanced in age; they may already be receiving medications for co-morbid diseases. Drug interactions can cause many clinical problems, particularly when the drugs are administered in combination with anticancer agents. On the other hand, there are many possible interactions between coumarins and other drugs. The mechanisms of these interactions in-

cluded absorption alterations and inhibition/induction of metabolic enzymes. Gefitinib is metabolized extensively in the liver, predominantly by CYP3A4 and CYP2D6. Furthermore, gefitinib has been reported to have a weak inhibitory effect on CYP1A2, CYP2C9 and CYP3A4 activities[12]. These results suggest that at least in some patients, gefitinib would inhibit the metabolism of acenocumarol, which is a substrate of CYP1A2, CYP2C9 and CYP2C19[5]. Furthermore, as gefitinib and acenocumarol are both highly proteins bound, gefitinib will also compete with acenocoumarol for albumin-binding sites, resulting in elevated levels of unbound acenocoumarol. Strict medical monitoring is required in clinical situations that can reduce protein binding of acenocoumarol, such as tumours or renal diseases. In conclusion, pharmacokinetic and pharmacodynamic interactions seem to occur between gefitinib and acenocoumarol. Reports of changes in the effects of oral anticoagulants coinciding with chemotherapy administration are many and variable[6-8]. However, the effect of oral antineoplasic agents is unknown. A case report (also Asian patients) of a warfarin-gefitinib interaction and drug dose reduction of the former has been found[13]. In our patient, after a month of exposure to gefitinib, INR increased to more than 8. Then, after a single-dose oral administration of gefitinib, INR increased again with no other clinical changes. Acenocoumarol dose was reduced to a quarter of the initial dose.

Conclusions

As there is a possibility of INR abnormalities ocurring during the concomitant use of gefitinib and acenocumarol as well as a marked inter-individual variability, clinicians should be aware of this interaction. The recommended patients' management is to closely monitor for changes in the effects of coumarin derivatives, if administered concomitantly with antineoplastic agents. Finally, acenocoumarol dose adjustment may be needed for patients receiving gefitinib.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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