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Interaction with St. John's wort due to exposure with blackcurrant aroma? How not to present a case report of an adverse event

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Background: Adverse events case reports are important for signal generation in pharmacovigilance. They require a thorough collation of the facts, otherwise they may lead to erroneous conclusions which may conceal other treatment-related causes of the observation. *Methods:* We describe a case report from the literature that arrives at an erroneous conclusion merely from taking insufficient care when collating and interpreting the facts: The authors of the case report confused blackcurrant (*Ribes nigrum*) with St. John's wort preparation (*Hypericum perforatum*) and erroneously assumed that the intake of a herbal preparation was responsible for a drop in serum levels of everolimus. *Results:* The clinical observations in this case report may actually reflect a potentially lethal situation emerging from the prescribed medication everolimus. St. John's wort preparations rich in hyperforin do in fact reproducibly lead to the decrease of blood levels of medications metabolized through cytochrome P450 subtype 3A4. However, a case report requires more care than just ascribing the blame to something seemingly well-known. *Conclusion:* The readers of this report might have profited more from the description of the risks of treating graft-versus-host disease with everolimus, and the action to be taken in case of potentially severe adverse reactions to everolimus.

1. Introduction

Cristóbal Gutiérrez et al. (2017) reported a clinical case of decreased blood levels of everolimus, supposedly caused by the concomitant intake of a St. John's wort preparation. The authors associate this observation with the St. John's wort constituent hypericin, presented as the cause for interactions through induction of cytochrome P450 subtypes 1A2 and 3A4. In this case, almost all of these assumptions are unfounded. The present work aims at documenting the underlying misinterpretations.

2. Investigations and results

The following details were given by the authors: A 66-year-old male patient diagnosed with myelodysplastic syndrome in August 2010 underwent a bone marrow transplant from a non-related subject in June 2011. The complications from the graft-versus-host disease (GvHD) were treated with the immunosuppressant medication tacrolimus, which then led to chronic kidney insufficiency. In June 2016, treatment of GvHD was switched to oral everolimus due to its better effects against chronic sclerodermiform GvHD, at a dose of 0.5 mg/12 h. The aim was to achieve a therapeutic blood concentration of 3-8 µg/l.

Already here, the reported details are conflicting: Figure 1 of the publication reports measurements in August 2017, Table 1 reports the same dates, but in 2016, and the text mentions the commencement of everolimus therapy in June 2016. We assume in the following that August 2016 was the correct date.

On August 5, a blood level of 1.9 µg/l was reached, which on August 9 was found more or less to be stable at 1.7 µg/l. As this was not deemed sufficient, the everolimus dose was increased to 1 mg/12 h, which had the intended effect: the blood level on August 16 had reached 3.3 µg/l. The subsequent measurements on August 25 and August 29 did, however, demonstrate the complete absence of detectable everolimus in the patient's blood. The patient was therefore specifically asked whether he had taken homeopathic or herbal preparations. The patient admitted having taken eight herbal lozenges of German origin (Isla Moos) daily for the treatment of cough for which onset coincided with the doubling of the everolimus dose and blood levels around the 16th of August 2016.

The authors of the report examined the package leaflet of the lozenges and were convinced of having found the presence of St. John wort extract from detecting the words "Schwarzer Johannisbeerextrakt" and "Schwarzes Johannisbeeraroma" and deducting that the word part "Johannis" must be equal to "St. John's". Having presumed this, the authors instructed the patient to immediately suspend the use of the lozenges because of the danger of an interaction.

Only a few days later everolimus was also suspended because of a sepsis of the respiratory tract and – according to the authors – pulmonary toxicity unlikely associated with everolimus, and more likely to represent a pulmonary picture of the GvHD. Due to the suspension of everolimus there were no further measurements of blood levels, and hence no proof of increasing blood levels after the suspension of the cough lozenges.

The authors link their observations to the presence of hypericin, pseudohypericin and flavonoids present in *H. perforatum* extracts, as, according to the authors, these substances are known inducers of cytochrome P450 1A2, 3A4, and glycoprotein P. Subsequently, the concomitant use of the herbal lozenges is not recommended as drug levels of everolimus may be reduced.

3. Discussion

Extract preparations from St. John's wort (*Hypericum perforatum*) are officially recognized as well-established in the treatment of mild to moderate major depression (HMPC 2009), but clearly not against cough – a discrepancy, which in the present case could

have raised some doubt. The use of St. John's wort is quite safe, with one important exception: some *H. perforatum* preparations enriched in hyperforin induce metabolic pathways involved in the clearance of drugs: such *H. perforatum* preparations have been consistently and reproducibly shown to activate the p-glycoprotein transporter (PGP) and cytochrome (CyP) P450. Within the group of CyP 450 subtypes, the clinically relevant effects are largely restricted to CyP 3A4, a metabolic enzyme responsible for the clearance of more than 50 % of all drug substances. There are other subtypes frequently proposed as additional pathways for interactions with *H. perforatum*, mainly CyP 1A2, but other subtypes than CyP 3A4 – especially CyP 1A2 – have never been shown to contribute to a clinically important mechanism of action for herb-drug interactions triggered by *H. perforatum*.

Moreover, the mechanisms of action and the constituent responsible for the interaction effect are clearly identified. It is neither the fraction of hypericins nor the flavonoids, as proposed by Cristóbal Guitérrez et al. (2017), that causes the problem, but the *H. perforatum* constituent hyperforin – and even then only when present in unnaturally high concentrations (around 4 %). Such concentrations can only be achieved when the plant material is harvested at the stage of fructification instead of, as traditionally done, full flowering. *H. perforatum* preparations low in hyperforin (≤ 3 %) do not or do not relevantly trigger an induction of CyP 3A4.

Furthermore, the multiple human interaction studies published to date consistently show that *H. perforatum* has to be applied for at least 2-3 weeks to cause a clinically important interaction. The reason for this delay lies in the mechanism of action of hyperforin: through an activation of the pregnane X receptor it causes an upregulation of the formation of cytochrome P450 3A4. Due to the *de novo* biosynthesis of CyP 3A4, this mechanism takes time to reach a trigger point from whereon the interaction becomes clinically important (Chrubasik-Hausmann et al. 2018; Thomsen et al. 2008; Moore et al. 2000; Wentworth et al. 2000; Schmidt et al. 2002; Schmidt and Butterweck 2015) .

In this case report the reaction occurred immediately after the intake of Isla Cassis, with a reduction of everolimus blood levels to zero in less than 9 days. This would be highly unusual. Even in the worst of described interactions with *H. perforatum* and hyperforin the blood levels of the concomitant medication never dropped to zero (Chrubasik-Hausmann 2018). A complete disappearing of everolimus from the patient's blood should rather have caused doubts with respect to the patient's compliance.

The most important misjudgement of this case report is, however, the supposed use of a *H. perforatum* preparation. The preparation claimed to be responsible for the observed drug interaction was the German cough lozenges product "Isla Cassis". The authors gave a reference to the product's composition in citation No. 3. The leaflet is available on the internet at https://www.engelhard.de/fileadmin/pdfs/Isla-Cassis.pdf. Each lozenge contains 80 mg of an aqueous extract of Iceland moss (*Cetraria islandica*, drug-extract ratio 0.4-0.8:1). Further constituents and excipients are – in decreasing order – ascorbic acid, sorbitol, gum Arabic, maltitol, citric acid, acesulfam K, "schwarzer Johannisbeerextrakt" = blackcurrant extract, "schwarzes Johannisbeeraroma" = blackcurrant aroma, paraffin and purified water. St. John's wort is quite obviously not a constituent of the lozenges, and taking into account that (in accordance to the standing rules of drug regulation) the quantity of excipients is descending in the order of their declaration, it becomes clear that blackcurrant extract and aroma is no more than a trace element in the lozenges. There was less blackcurrant extract and aroma than the artificial sweetener acesulfam K, a substance used in the low milligram range. The blackcurrant preparations therefore only serve as a flavour. Even if St. John's wort had been present, the quantity would not have been sufficient to trigger an interaction.

The authors of the case report obviously mistook the German vernacular name for blackcurrant = "Johannisbeere" for St. John's wort = "Johanniskraut". Blackcurrants are the edible fruits of *Ribes nigrum*, family Grossulariaceae – the plant family of gooseberries which includes kiwi fruits among many other food plants. The German name part "Johannis", "St. John's" refers to the period of the year when the first berries may be harvested: the 24th of June is the St. John's day of old. "Johanniskraut" = St. John's wort is biologically completely unrelated. *Hypericum perforatum* of the family of Clusiaceae typically flowers around June 24th, hence the name "Johanniskraut", St. John's wort, but has otherwise nothing in common with "Johannisbeere", black-currant. With St. John's wort not even present in the lozenge preparation reported in this case, it cannot be held responsible for the observation of a drop of blood levels of everolimus. Neither can this observation or any other herb-drug interaction be associated with an absolutely implausible interaction with hypericin or flavonoids.

As already stated, even if the lozenge preparation had consisted of 100 percent hyperforin instead of none at all, it would be extremely unusual if CyP 3A4 were activated within only nine days and to a degree of 100 % reduction of blood levels – this has never been observed before.

There must be another explanation for the incident. One possible explanation might be related to the effects of everolimus itself. According to the listing of adverse effects of everolimus, this active pharmaceutical ingredient causes respiratory tract infections and cough in 30 % of patients. In the typical wording of pharmacovigilance this adverse effect is considered "very common" (see www.drugs.com). The Summary of Product Characteristics (SPC) provided for the medication "Afinitor tablets" by the European Medicines Agency (www.ema.europa.eu) states as a precautionary measure that in case of the occurrence of non-infectious pneumonitis a treatment interruption or even discontinuation must be considered. According to the authors of the case report, a respiratory sepsis and pulmonary toxicity reluctantly associated with everolimus were the reason for the ultimate discontinuation of the drug – ultimately doing what the SPC was recommending for the situation present days before. As a matter of fact, the patient started complaining about cough just after the dose of everolimus was doubled – one would expect that a symptom strong enough for the patient to seek help by using cough lozenges should not have passed unnoticed and unquestioned on the day of the examination on August 16th, 2016.

The occurrence of cough and respiratory complications such as pneumonitis is not only a major drawback of everolimus treatment, but was most likely also the indication for the use of the Iceland moss lozenges. The question is therefore, whether the patient had not simply stopped everolimus intake because of the occurrence of respiratory complications, which were then self-treated with cough lozenges. According to the authors the compliance was estimated to be 100 percent until the start of intake of *Isla Cassis*, which by itself should have pointed to the presence of a respiratory disease. The start of the intake of *Isla Cassis* coincided with the start of the drop of blood levels of everolimus. It seems that the patient was asked whether he took other medications, but not whether he had continued the intake of everolimus at or after this point. As stated above, an immediate discontinuation would have been the logical consequence of the occurrence of respiratory symptoms – and the measure recommended by the SPC! The severe consequence of a sepsis and bronchial toxicity might perhaps have been avoided if the physicians had acted in time.

As proposed herein, the reduction of everolimus serum levels to zero rather seems to point towards an early discontinuation of everolimus triggered by the occurrence of respiratory adverse effects. As St. John's wort was not present in this case, it could not have been responsible for the change in serum levels, and neither could Iceland moss or blackcurrant flavouring – the latter being of very small quantities only. Neither are known to cause interactions by CyP 3A4 induction. The causality assessment given by the authors is therefore obviously premature at best or completely erroneous at worst. Even worse still, it may contribute to an underreporting of adverse effects of the medication everolimus prescribed by the authors, and to belated reactions in aggravating clinical situations.

Case reports of adverse events are very important tools in pharmacovigilance. The relatively small scale controlled clinical

trials in artificially selected patient populations used in phase III marketing authorisation studies do not typically produce a complete list of possible adverse reactions of an active pharmaceutical ingredient. Physicians' experiences and observations are valuable contributions to the development of a fuller drug monograph by providing early signals of previously unknown adverse effects. It is therefore of utmost importance that physicians share their observations.

However, such observations should follow a certain scientific standard. They require a minimum amount of literature research. If, as in the present case, the report is merely built on a sequence of poor deductions and assumptions which are not corroborated by an exhaustive bibliographic evidence, wrong conclusions can be drawn. The goal of increasing awareness towards pharmacovigilance issues is then clearly not achieved. Quite the contrary, they may result, as in this specific case, in a masking of severe adverse reaction of everolimus.

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