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WHO Collaborating Centre for International Drug Monitoring

SIGNAL

Analyses of Reports in the WHO Global ICSR Database – VigiBase® · April 2015

Signals in this issue

- Atomoxetine – Dystonia
- Atomoxetine – Neutropenia
- Desloratadine – Aggressive reaction
- Dextromethorphan – Serious neurological disorders
- HPV vaccine – Gastrointestinal motility disorders
- Olanzapine – Accidental drug intake by children
- Prucalopride – Suicidal ideation
- Temozolomide – Oesophagitis
- Vemurafenib – Thrombocytopenia

Uppsala Monitoring Centre

Please direct all correspondence regarding signals presented in this document to the Uppsala Monitoring Centre

SIGNAL

Potentially interesting pharmacovigilance signals assessed by the UMC Review Panel

The WHO has defined a signal as:
"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously" An additional note says: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another. A signal may also be more documentation which further qualifies a simple association of a drug product with an ADR, for examples, information on the range of severity of reaction, its outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or indeed a lack of such an effect by a particular drug.

SIGNAL is edited and produced by the Uppsala Monitoring Centre (UMC) and presents information derived from the WHO Global ICSR Database. This database contains summaries of case reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres (NCs) in about half the countries of the world. More information regarding these data, their limitations and proper use, is provided in the Caveat on the last page of this document.

The UMC Review Panel consists of international, experienced scientists, usually affiliated to a governmental or academic institution or a pharmaceutical company, invited by the UMC. They assess – under the responsibility of the UMC – the database for the occurrence of signals of possible importance for public health, drug regulation and science.

The topics discussed in SIGNAL are thus varying levels of suspicions derived from examination of the data in the UMC database. As emphasised above, SIGNAL contains different hypotheses, primarily intended to inform national regulatory authorities, which may in turn consider the needs for possible further action (for instance further evaluation of source data, or a study for the testing of a hypothesis). The distribution of SIGNAL by the UMC is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme for International Drug Monitoring and to international pharmaceutical companies which can be identified as uniquely responsible for the drug concerned. The UMC takes no responsibility for contacting all market authorisation holders.

National authorities and NCs are responsible for deciding on further action including communicating the information in SIGNAL to relevant health professionals, and to the responsible market authorisation holders, within their jurisdictions.

In order to further a healthy debate, we encourage all recipients of SIGNAL to comment briefly (about 1000 words) on individual topics. The comments will be published in the next available edition.

** Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.*

Content of SIGNAL April 2015

Source information

IMS LIFECYCLE 2013 has been used as a source of information regarding the licensor/patent holders, to which certain signals have been submitted for comments.

Responses from industry

Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

Editorial Team

Pia Caduff-Janosa, Rebecca E Chandler, Sara Hult, Lovisa Sandberg, Daniele Sartori, Sarah Watson

Editorial

Kristina Star, Uppsala Monitoring Centre

This first edition of SIGNAL for 2015 is proud to present the first signals generated from the first large-scale signal detection screening of reports on children in VigiBase®. Safety of medication use in the paediatric population has been a major research focus for the UMC in recent years,[1] so the generation of child specific signals is a significant milestone and reflects our ambition to bring novel methods rapidly to real-world use.

For five days in September 2014 the UMC's Research Section reviewed drug and adverse reaction combinations reported specifically for children. The combinations for each paediatric age group (0-27 days, 28 days-23 months, 2-11 years, 12-17 years) were prioritized according to vigiRank, which takes into account disproportionality, quality and content of the individual reports.[2] The signal detection screening was based on a paediatric data subset, but other ages were considered as well in the in-depth assessment of the case series. We were fortunate to have Emeritus Professor Imti Choonara, a paediatric clinical pharmacologist from the University of Nottingham in the UK, with us as a consultant for part of the signal detection work week.

Nineteen combinations were identified for further assessment. Evaluations are still under way, but three of these combinations are presented in this edition. Also included are two short summaries of concerns for adverse reactions reported in connection to off-label medication use and accidental drug intake by children.

Another feature of this edition of SIGNAL is that it presents the first signals detected in a selected population. Future editions will incorporate signals from other focus groups, and we hope that our new approach will be a valuable complement to the national pharmacovigilance centres' own signal detection.

In addition to the paediatric signals already mentioned, this edition also presents four other signals generated in 2014, including one vaccine signal.

1. Star K, Noren GN, Nordin K, Edwards IR. Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase. Drug Saf. 2011;34(5):415-28.
2. Caster O, Juhlin K, Watson S, Noren GN. Improved statistical signal detection in pharmacovigilance by combining multiple strength-of-evidence aspects in vigiRank: retrospective evaluation against emerging safety signals. Drug Saf. 2014;37(8):617-28.

Note!

The number of reports mentioned in these signals may differ from the number of reports shown in VigiLyze when applying the same time scope. This is due to a recent update of WHO-ART, which includes changes in the structure of terms and in the MedDRA-WHO-ART mapping bridge. Some preferred terms have been merged, and some included terms have been upgraded to a preferred term or moved to another preferred term.

Atomoxetine and Dystonia in paediatric patients

Dr. Ian Boyd, Australia

Summary

Atomoxetine is a relatively potent inhibitor of the presynaptic noradrenaline transporter, a moderate inhibitor of 5HT uptake, and a weak inhibitor of dopamine uptake with minimal affinity for the other noradrenergic receptors. It is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as defined by DSM-IV criteria in children 6 years of age and older, adolescents and adults. After the elimination of suspected duplicates there are currently (1 September 2014) 31 individual case safety reports (ICSRs) in the WHO Global ICSR database, VigiBase® of dystonia in association with atomoxetine for children and adolescents up to 17 years of age. The reports are from Australia, Canada, Germany, Italy, Japan, New Zealand, South Africa, Spain, Switzerland and the United States. Atomoxetine was the only drug suspected in 21 of the 31 cases. The outcome of the dystonia was indicated in 17 reports. The patients were reported as recovered or recovering in 16 cases and not recovered in the remaining case. In the cases where recovery was reported, the drug was withdrawn in 13 cases, continued in one case and the fate of the drug was unknown in the remaining two cases.

Case reports in VigiBase suggest that there is a possible signal for the association of atomoxetine and dystonia. The fact there was a positive dechallenge in 13 of the 16 reports where recovery was documented is suggestive of a drug-induced effect. However, the possible association of atomoxetine with dystonia appears restricted to the adolescent and paediatric population. A possible mechanism may be based on inhibition of dopamine uptake.

Introduction

Atomoxetine is a relatively potent inhibitor of the presynaptic noradrenaline transporter, a moderate inhibitor of 5HT uptake, and a weak inhibitor of dopamine uptake with minimal affinity for the other noradrenergic receptors. Atomoxetine has moderate affinity for 5HT2 and GABAA receptors but poor affinity for most other receptors. It is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as defined by DSM-IV criteria in children 6 years of age and older, adolescents and adults. The most frequent adverse reactions reported during clinical trials of atomoxetine in children and adolescents include gastrointestinal reactions, increased blood pressure and heart rate, decreased appetite, decreased weight and skin reactions. Common neuropsychiatric reactions reported included dizziness, mood swings, somnolence, insomnia, irritability and depression.[1]

Dystonia denotes abnormal movements that are slow or so sustained that they may appear as abnormal postures. These abnormal movements of groups of muscles or body segments include grimacing, torticollis, blepharospasm and limb torsions. Generally, they are absent during sleep and exacerbated by emotional stress or voluntary activity. Dystonia occurs as an occasional complication of treatment with neuroleptic and dopaminergic drugs and many others. Drug-induced dystonia may be early (onset within one week of commencement of treatment) or late (onset after several weeks, months or years of treatment). Late persistent dystonia is usually termed tardive dyskinesia.[2]

Dystonia is a preferred term in WHO-ART with a number of included terms including trismus and various spasms (facial, infantile, cervical, oropharyngeal, tongue).

Reports in VigiBase

As of 1 September 2014, after the elimination of suspected duplicates, there are a total of 40 individual case safety reports (ICSRs) of dystonia in association with atomoxetine in the WHO Global ICSR database, VigiBase®. Out of these reports there are 31cases of dystonia in children and adolescents up to 17 years of age (Table 1). Of the remaining reports one is a 51 year old and one a 24 year old and the rest are have reported age unknown. The reports from children and adolescents were submitted from the United States (20 reports), Australia (2), South Africa (2), Canada, Germany, Italy, Japan, New Zealand, Spain and Switzerland (1 each). The patients ranged in age from 5 to 17 years with a median of 9 years. There were 23 males and 8 females.

Atomoxetine was the only drug suspected in 21 of the 31 cases. There were other drugs also suspected in the remaining 10 cases and they included drugs for treatment of psychotic disorders in seven cases, drugs for treatment of depression (3 cases), epilepsy (3 cases) and ADHD (3 cases). In seven of these 10 cases, at least one of these drugs (olanzapine, ziprasidone, risperidone, chlorpromazine) is a likely cause. Antipsychotic drugs are a well-known cause of dystonia

Table 1. Case overview of reports from children and adolescents in VigiBase® of dystonia in association with atomoxetine

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reactions (WHO-ART preferred terms)	Outcome
1	10/M	Buspirone, citalopram, diphenhydramine, methylphenidate, risperidone, valproic acid (all C)	Dystonia, drug interaction, drug level decreased, EEG abnormal, muscle contractions involuntary, saliva increased, somnolence, mental status changes*	Unknown
2	16/F	Olanzapine (S) Valproic acid (C)	Dystonia, coma, tongue disorder	Unknown
3	10/M	Fluvoxamine, quetiapine (both C)	Dystonia, agitation, anxiety, asthenia, nausea, paraesthesia, SGOT increased, somnolence, drug level changed*, pain in extremity*	Recovered
4	7/M	None	Dystonia, abdominal pain, azotaemia, dyskinesia, eye abnormality, fever, hypercalcaemia, leukocytosis, opisthotonos, pharyngitis, phosphatase alkaline increased, therapeutic response decreased, varicella, vomiting, eye injury*, eye penetration*, treatment noncompliance*	Unknown
5	9/F	Olanzapine (S) Dexamfetamine sulfate/amfetamine sulfate/dexamfetamine saccharate/ amfetamine aspartate (C)	Dystonia, therapeutic response increased	Recovered
6	16/F	Dexamfetamine sulfate/amfetamine sulfate/dexamfetamine saccharate/ amfetamine aspartate (C)	Dystonia, hallucination, medication error, muscle contractions involuntary	Recovered
7	15/F	Dexamfetamine sulfate/amfetamine sulfate/dexamfetamine saccharate/ amfetamine aspartate (C)	Dystonia, diplopia, hallucination, medication error, muscle contractions involuntary, mydriasis, self-medication*	Recovered
8	16/F	Levosalbutamol (C)	Dystonia, blepharospasm, dizziness, drug interaction, hypokinesia, speech disorder, tremor	Unknown
9	8/F	Risperidone (C)	Dystonia	Recovered
10	12/F	None	Dystonia, blepharospasm, dyskinesia, pruritus, therapeutic response decreased	Recovered
11	9/M	Bupropion, oxcarbazepine, quetiapine, risperidone, valproic acid (all S)	Dystonia	Unknown
12	9/M	Methylphenidate, ziprasidone (both S) Valproic acid (C)	Dystonia, anorexia, choreoathetosis, convulsions grand mal, saliva increased, jaw disorder*	Recovered
13	10/M	Oxybutynin (S)	Dystonia, drug interaction, dyspnoea, extrapyramidal disorder, face oedema, mental deficiency, muscle contractions involuntary, musculoskeletal disorder, neuralgia, pain, skeletal pain, speech disorder, tachycardia, tenderness NOS, tetany	Recovered
14	17/M	Guaifenesin/dextromethorphan hydrobromide (C)	Dystonia, tachycardia, therapeutic response increased, amphetamines positive*	Unknown
15	13/M	None	Dystonia, condition aggravated, muscle contractions involuntary	Recovered
16	8/M	None	Dystonia, medicine ineffective, muscle contractions involuntary	Recovering
17	10/M	Risperidone, sertraline (both C)	Dystonia, dysphagia, accident NOS	Unknown
18	8/M	Loratadine (C)	Dystonia, abdominal pain, dizziness, insomnia, muscle contractions involuntary, nausea, somnolence	Recovered
19	5/M	Risperidone (C)	Dystonia, muscle contractions involuntary	Unknown
20	11/M	Lamotrigine (C)	Dystonia	Not recovered
21	6/M	None	Dystonia, extrapyramidal disorder, muscle contractions involuntary, jaw disorder*	Unknown
22	15/M	None	Dystonia, paraesthesia	Recovered
23	15/F	Fluoxetine (S) Bupropion, fluoxetine (both C)	Dystonia, agitation, amnesia, anxiety, coma, convulsions grand mal, headache, hypertension, oculogyric crisis, tachycardia, urinary incontinence, tongue biting*	Unknown
24	9/M	Methylphenidate (S)	Dystonia, extrapyramidal disorder	Unknown

25	5/M	Risperidone (S) Valproic acid (C)	Dystonia	Recovered
26	9/M	Acetylsalicylic acid, risperidone, valproic acid (S)	Dystonia, dyskinesia	Unknown
27	8/M	Periciazine (C)	Dystonia	Recovered
28	9/M	Fluticasone, paracetamol, salbutamol, salmeterol (C)	Dystonia, anxiety	Recovered
29	13/M	Risperidone (C)	Dystonia, diarrhoea bloody, extrapyramidal disorder, fatigue, gastritis, hepatic enzymes increased, oedema generalised, urine abnormal, vomiting, weight decrease	Unknown
30	5/M	Amfetamine, aripiprazole, carbamazepine, chlorpromazine, clonidine, dexamfetamine, iloperidone, lisdexamfetamine, lithium, methylphenidate, quetiapine, valproic acid, ziprasidone (S)	Dystonia, aggressive reaction, anxiety, choreoathetosis, crying abnormal, coordination abnormal, depression, dyskinesia, emotional lability, fatigue, hyperkinesia, infection bacterial, insomnia, medicine ineffective, nervousness, sleep disorder, speech disorder, suicide ideation, teeth-grinding, decreased eye contact*, homicidal ideation*, oppositional defiant disorder*	Unknown
31	5/M	Risperidone (S)	Dystonia, convulsions	Recovered

NOS = Not otherwise specified
**MedDRA terms*

and the four drugs listed above all refer to dystonia as a possible adverse effect in their product information.[3] Concomitant drugs were reported in 20 of the 31 cases and showed a similar trend to that observed with the co-suspected drugs with considerable use of antipsychotic, anticonvulsant, and antidepressant drugs along with the use of other treatments for ADHD.

Time to onset was reported in only two of the reports and ranged from the same day the drug was administered to 24 days. The outcome of the dystonia was indicated in 17 reports. The patients were reported as recovered or recovering in 16 cases and not recovered in the remaining case. In the cases where recovery was reported, the drug was withdrawn in 13 cases, continued in one case and the fate of the drug was unknown in the remaining two cases. In the case where the patient had not recovered, the drug was continued.

The indication for use was stated in 23 reports and indicated ADHD or a related disease in all 23 cases. Dosage ranged from 10 mg to 160 mg (median: 25 mg) in the 16 cases which reported this information.

Other reactions were reported in 26 of the 31 reports. Other neuropsychiatric reactions were reported in 23 of those reports and six reports described gastrointestinal reactions. Changes in drug levels, changes in therapeutic response or medicine ineffective were reported in eight cases.

Literature and Labelling

The product literature does not refer to dystonia although it does mention that very common, common or uncommonly reported neurological reactions included headache, dizziness, somnolence including sedation, insomnia, syncope and tremor. Post-marketing adverse neurological events reported very rarely include seizures, paraesthesia in children and adolescents, hypoaesthesia and tics.[1] No reports of dystonia in association atomoxetine could be found in the literature.

Discussion

Case reports in VigiBase suggest that there is a possible signal for the association of atomoxetine and dystonia in children and adolescents. Atomoxetine was the only drug suspected in 21 of the 31 cases. In the remaining 10 cases, other suspected drugs would appear to be a more likely cause in seven reports but atomoxetine would appear an equally likely cause in the other three cases.

Time to onset was reported in only two of the reports and ranged from the same day the drug was administered to 24 days. The outcome of the dystonia was indicated in 17 reports. The patients were reported as recovered or recovering in 16 cases and not recovered in the remaining case. In the cases where recovery was reported, the drug was withdrawn in 13 cases, continued in one case and the fate of the drug was unknown in the remaining two cases. In the case where the patient had not recovered, the drug was

continued. The fact there was a positive dechallenge in 13 of the 16 reports where recovery was documented is suggestive of a drug-induced effect.

The possible association of atomoxetine with dystonia appears restricted to the adolescent and paediatric population. There is a total of 33 reports of dystonia in association with atomoxetine in the total population where the age is known. Thirty-one of these reports were reported in the adolescent and paediatric age groups which represents 93.9% of all the reports. While it may be considered that atomoxetine is used preferentially in the younger age groups, overall reporting in VigiBase indicates that of the 16,592 reports submitted, the age group from 2 to 17 years represents 72.3% of the total reports in which the age is known.

The pathophysiological mechanisms underlying acute extrapyramidal symptoms such as dystonia are usually attributed to the effects of dopamine receptor blockade in the basal ganglia.[4] As atomoxetine is a weak inhibitor of dopamine uptake, it is possible that this may be the basis of a possible mechanism. It is also possible that children and adolescents may be at greater risk as it is known that younger age is a risk factor for the development of dystonia in patients receiving antipsychotic treatment.[3]

Conclusion

In summary, there are 31 reports associating dystonia with the use of atomoxetine from children and adolescents. Atomoxetine was the only drug suspected in 21 of the 31 cases. The fact there was a positive dechallenge in 13 of the 16 reports where recovery was documented is suggestive of a drug-induced effect. However, the possible association of atomoxetine with dystonia appears restricted to the adolescent and paediatric population. A possible mechanism may be based on inhibition of dopamine uptake.

References

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2. The Council for International Organizations of Medical Sciences (CIOMS). Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for their Use. CIOMS, Geneva, 1999. URL: http://www.cioms.ch/publications/reporting_adverse_drug.pdf. Accessed: 30 January 2015.
3. Jimenez-Jimenez FJ, Garcia-Ruiz PJ, Molena JA. Drug-induced movement disorders. Drug Safe 1997;16:180-204.
4. Casey DE. Neuroleptic drug-induced extrapyramidal symptoms and tardive dyskinesia. Schizo Res 1991;4:109-20.

Response from Eli Lilly & Company

Thank you for the opportunity to provide our comments on the thorough assessment conducted by Dr. Boyd. Eli Lilly & Company (Lilly) routinely queries reported adverse events in databases (Lilly's internal safety database and FDA Adverse Event Reporting System) for early signs of potential adverse drug reactions in patients treated with Lilly drugs. Lilly recognizes the importance of early signal detection and also acknowledges that database queries are only one method that can be employed. Additionally, Lilly's reviews of the spontaneously reported adverse events involve medical assessment of the narratives where information provided and not captured in the standard fields often helps to refine the assessment.

Consistent with the Uppsala Monitoring Centre, Lilly recognizes that signals are uncertain and preliminary in nature (Uppsala Monitoring Centre, Signals selected by UMC and the clinical review panel: How the process works). This is because, for any given adverse event report considered in generating a signal, there is no certainty that the adverse event was caused by the suspected drug. Rather, the adverse event could have resulted from the underlying condition being treated, a comorbid condition, a concomitant medication, or may simply be the result of chance.

Treatment-emergent dystonias have been associated with reduced dopamine neurotransmission in the basal ganglia, as typically described with antipsychotic medications such as risperidone or quetiapine (Tarsy and Simon, 2006). In this respect, it is pertinent that atomoxetine and other attention deficit hyperactivity disorder (ADHD) medications are not infrequently given in conjunction with concomitant medications including antipsychotic medications to treat the commonly occurring comorbid conditions associated with ADHD. Furthermore, as Dr. Boyd mentioned in his assessment, younger individuals may be at greater risk of developing dystonia when they receive antipsychotic treatment. Lilly agrees with Dr. Boyd's observation that in seven of the 31 cases co-suspect antipsychotic medications were a likely cause. Lilly also agrees with Dr. Boyd`s comment that, upon review of the data in Table 1, concomitant drugs were reported in 20 of the 31 cases and that these showed a similar trend to that observed with the co-suspected drugs with considerable use of antipsychotic, anticonvulsant, and antidepressant drugs. This observation seems to indicate that, although not considered suspect per se, many cases involved concomitant medications that have been associated with dystonic or other similar movement effects and hence, may also possibly be confounded.

Based on in vivo preclinical data, atomoxetine enhances dopamine release in the prefrontal cortex, but not in the basal ganglia (i.e. striatum; Bymaster et al. 2002). Therefore, the mechanism by which atomoxetine could stimulate an induced dystonia via the dopaminergic pathway is unclear.

In the current report, no rechallenge information was included, so Lilly presumes that none of the case reports involved a rechallenge situation. Positive dechallenge was, however, described in 13 of the 16 reports where recovery was documented. The significance of this information is not entirely clear as it was not mentioned if atomoxetine alone was stopped or if any concomitant medications (neuroleptics, antidepressants, stimulants, or other drugs) were stopped at the same time as atomoxetine or if the dystonia events may have been treated with pharmacological intervention. All of these factors would confound the assessment.

Although Lilly regularly conducts ongoing surveillance, including automated signal detection for all its medications, Lilly has not previously identified a signal for dystonia with atomoxetine from any of our available data sources, including clinical trials. As noted in Dr. Boyd`s evaluation, no reports of dystonia in association with atomoxetine could be found in the literature. Nevertheless, Lilly takes the information provided by the Uppsala Monitoring Centre seriously, and therefore, based on the possible signal reported by Dr. Boyd, plans to conduct a comprehensive review of dystonia events in atomoxetine-treated patients.

References

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Atomoxetine and Neutropenia in paediatric patients

Dr. Ian Boyd, Australia

Summary

Atomoxetine is a relatively potent inhibitor of the presynaptic noradrenaline transporter, a moderate inhibitor of 5HT uptake, and a weak inhibitor of dopamine uptake with minimal affinity for the other noradrenergic receptors. It is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as defined by DSM-IV criteria in children 6 years of age and older, adolescents and adults. After the elimination of duplicates, there are currently (4 February 2015) 25 individual case safety reports (ICSRs) in the WHO Global ICSR database, VigiBase® of neutropenia in association with atomoxetine in children and adolescents. The reports are from Canada, Finland, Germany, Ireland, Switzerland, the United Kingdom and the United States. Atomoxetine was the only drug suspected in 20 of the 25 cases. The outcome of the neutropenia was indicated in 15 reports. The patients were reported as recovered or recovering in 10 cases and not recovered in the remaining five cases. In the cases where recovery was reported, the drug was withdrawn in seven cases, the dose increased in one case and the fate of the drug was unknown in the remaining two cases. Time to onset showed a clustering around 14-27 days.

Case reports in VigiBase suggest that there is a possible signal for the association of atomoxetine and neutropenia. The fact there was a positive dechallenge in seven of the 10 reports where recovery was documented is suggestive of a drug-induced effect. This is supported by the time to onset of 14-27 days which is consistent with drug-induced neutropenia. However, the possible association of atomoxetine with neutropenia appears predominantly in the adolescent and paediatric population.

Introduction

Atomoxetine is a relatively potent inhibitor of the presynaptic noradrenaline transporter, a moderate inhibitor of 5HT uptake, and a weak inhibitor of dopamine uptake with minimal affinity for the other noradrenergic receptors. Atomoxetine has moderate affinity for 5HT2 and GABAA receptors but poor affinity for most other receptors. It is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as defined by DSM-IV criteria in children 6 years of age and older, adolescents and adults. The most frequent adverse reactions reported during clinical trials of atomoxetine in children and adolescents including gastrointestinal reactions, increased blood pressure and heart rate, decreased appetite, decreased weight and skin reactions. The product information does not refer to blood disorders.[1]

Neutropenia is a high level term in WHO-ART with preferred terms consisting of neutropenia, granulocytopenia and leukopenia.

The preferred term, neutropenia, which is the subject of this signal, is defined as a decrease to less than 1.5 x 10^9/L of segmented polymorphonuclear and band cells. Neutropenia is considered as "severe" below 0.5 x 10^9/L.[2]

Reports in VigiBase

As of 4 February 2015, there are a total of 35 individual case safety reports (ICSRs) of neutropenia in association with atomoxetine in the WHO Global ICSR database, VigiBase®. Out of these reports, after the elimination of duplicates, there are 25 cases of neutropenia in children and adolescents up to 17 years of age (Table 1). Of the remaining reports, ages range from 22 years to 65 years in seven cases and the remaining case has reported age unknown. The reports from children and adolescents were submitted from the United Kingdom (9 reports), United States (7), Finland (4), Canada (2), Germany, Ireland and Switzerland (1 each). The patients ranged in age from 6 to 17 years with a median of 12 years. There were 23 males and 2 females.

Atomoxetine was the only drug suspected in 20 of the 25 cases. There were other drugs also suspected in the remaining five cases and they included drugs for treatment of psychotic disorders (olanzapine, risperidone) in two cases, an antidepressant (fluoxetine) in one case, an anticonvulsant (valproic acid) in one case and another drug for the treatment of ADHD (methylphenidate) in the remaining case. Three of these drugs, olanzapine, risperidone and valproic acid, refer to neutropenia in their product information and these drugs may each be a possible cause in the three cases where these drugs are suspect (Cases 5, 7 and 24). Concomitant drugs were reported in 10 of the 25 cases and showed a similar trend to that observed with the co-suspected drugs with use of antipsychotic, anticonvulsant, and antidepressant drugs along with the use of other treatments for ADHD.

Table 1. Case overview of reports from children and adolescents in VigiBase® of neutropenia in association with atomoxetine

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reactions (WHO-ART preferred terms)	Outcome
1*	14/M	Sertraline (C)	Neutropenia, abdominal pain, bone marrow aplasia, fatigue, hepatitis, thrombocytopenia	Recovering
2	12/M	Pipamperone (C)	Neutropenia, anaemia, leukopenia, lymphocytes atypical	Unknown
3	12/M	Fluoxetine (S)	Neutropenia	Unknown
4	11/M	None	Neutropenia, alopecia, weight decrease	Recovered
5	14/M	Risperidone (S)	Neutropenia	Unknown
6*	14/F	Sertraline (C)	Neutropenia, hepatitis cholestatic, hepatic fibrosis, hepatitis viral, thrombocytopenia, educational problem***	Recovered
7	13/M	Olanzapine (S) Aripiprazole, escitalopram, guaifenesin (C)	Neutropenia, alkaline phosphatase increased, ALT increased, AST increased, lymphocytosis, monocytosis, blood calcium abnormal#, protein total abnormal***	Unknown
8	17/M	Valproic acid, sertraline (C)	Neutropenia, lymphocytosis	Unknown
9	9/M	None	Neutropenia, abdominal pain, flatulence, gastroenteritis, haematemesis, hypotension, intestinal obstruction, leukopenia, peripheral ischaemia, systemic inflammatory response syndrome, tachycardia, thrombocytopenia	Recovered
10	11/M	Methylphenidate (S)	Neutropenia, leukopenia	Unknown
11	16/M	None	Neutropenia, leukopenia	Recovering
12	10/M	None	Neutropenia, leukopenia, thrombocytopenia	Not recovered
13	11/M	None	Neutropenia, abdominal pain, agitation, anorexia, fatigue, hallucination, weight decrease	Recovered
14	12/M	Risperidone (C)	Neutropenia, leukopenia, weight decrease	Not recovered
15	12/F	None	Neutropenia, leukopenia	Recovered
16	11/M	None	Neutropenia, leukopenia	Recovered
17**	11/M	Salbutamol (C)	Neutropenia	Recovering
18	6/M	None	Neutropenia, leukopenia, rash	Recovered
19	7/M	Methylphenidate (C)	Neutropenia, peripheral ischaemia	Unknown
20	10/M	None	Neutropenia	Unknown
21**	11/M	Methylphenidate, salbutamol (C)	Neutropenia	Not recovered
22	11/M	None	Neutropenia, alkaline phosphatase increased, hypotension postural, urticaria	Recovered
23	15/M	Methylphenidate (C)	Neutropenia	Not recovered
24	14/M	Valproic acid (S) Valproic acid (C)	Neutropenia, bilirubinaemia, epilepsy, lymphopenia, thrombocytopenia, weight decrease	Not recovered
25	12/M	Melatonin, methylphenidate (C)	Neutropenia	Not recovered
26	15/M	None	Neutropenia, leukopenia	Unknown
27	10/F	None	Neutropenia, ALT increased, anaemia, AST increased, blood disorder, Epstein-Barr virus, hepatic function abnormal, hepatomegaly, monocytopenia, thrombocytopenia	Unknown

**Cases 1 and 6 are duplicates*

***Cases 17 and 21 are duplicates*

****MedDRA terms*

Time to onset was reported in 11 of the reports and ranged from 14 days to 10 months. The median time was 50 days and there was a clustering of five cases between 14 and 27 days.

The outcome of the neutropenia was indicated in 15 reports. The patients were reported as recovered or recovering in 10 cases and not recovered in the remaining five cases. In the cases where recovery was reported, the drug was withdrawn in seven cases, the dose was increased in one case and the fate of the drug was unknown in the remaining two cases. In the five cases where the patient had not recovered, the drug had been discontinued in four cases and the fate of the drug was unknown in the remaining case.

The indication for use was stated in 15 reports and was ADHD in all 15 cases. Dosage ranged from 18 mg to 100 mg including some cases in which the dose was escalated.

Other reactions were reported in 19 of the 25 reports. Other blood disorders were reported in 15 of these cases and these were mostly other white cell disorders, particularly leucopenia, in 14 cases although thrombocytopenia was reported in five cases and red cell disorders in three cases. Hepatic reactions were reported in five cases and weight decrease was reported in four cases.

Literature and Labelling

The product literature does not refer to neutropenia nor does it mention other blood disorders.[1] No reports of neutropenia in association with atomoxetine could be found in the literature.

Discussion

Case reports in VigiBase suggest that there is a possible signal for the association of atomoxetine and neutropenia in children and adolescents. Atomoxetine was the only drug suspected in 20 of the 25 cases. In three of the remaining five cases, there were co-suspected drugs for which neutropenia is labelled.

Time to onset was reported in 11 of the reports and ranged from 14 days to 10 months. The median time was 50 days and there was a clustering of five cases between 14 and 27 days. This is consistent with drug-induced neutropenia.

The outcome of the neutropenia was indicated in 15 reports. The patients were reported as recovered or recovering in 10 cases and not recovered in the remaining five cases. In the cases where recovery was reported, the drug was withdrawn in seven cases, the dose was increased in one case and the fate of the drug was unknown in the remaining two cases. In the five cases where the patient had not recovered, the drug had been discontinued in four cases and the fate of the drug was unknown in the remaining case. The seven cases with a positive dechallenge is supportive of a drug-induced effect. The reports without recovery may simply represent cases that have been reported before the reaction had resolved. Drug-induced neutropenia usually resolves after 10 days.[3]

The possible association of atomoxetine with neutropenia appears predominantly in the adolescent and paediatric population. After the elimination of duplicates, there is a total of 33 reports of neutropenia in association with atomoxetine in the total population. Twenty-five of these reports were reported in the adolescent and paediatric age groups which represents 75.8% of all the reports. While it may be considered that atomoxetine is used preferentially in the younger age groups, overall reporting in VigiBase indicates that of the 16,504 reports submitted, the age group from 2 to 17 years represents 60% of the total reports.

Conclusion

In summary, there are 25 reports from children and adolescents associating neutropenia with the use of atomoxetine. Atomoxetine was the only drug suspected in 20 of the 25 cases. The fact there was a positive dechallenge in seven of the 10 reports where recovery was documented is suggestive of a drug-induced effect. The clustering of five cases with an onset between 14 and 27 days is consistent with drug-induced neutropenia. However, the possible association of atomoxetine with neutropenia appears predominantly in the adolescent and paediatric population.

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Response from Eli Lilly & Company

Thank you for the opportunity to provide our comments on the possible signal that has been generated from the Uppsala Monitoring Centre`s VigiBase safety database and the thorough assessment conducted by Dr. Boyd. Eli Lilly & Company (Lilly) routinely queries reported adverse events in Lilly's internal safety database and the FDA Adverse Event Reporting System for early signs of potential adverse drug reactions in patients treated with Lilly drugs. Lilly recognizes the importance of early signal detection and also acknowledges that database queries are only one method that can be employed. Additionally, Lilly's review of the reported adverse events involves medical assessment of the narratives where information provided and not captured in the standard fields often helps to refine the assessment.

Consistent with the Uppsala Monitoring Centre, Lilly recognizes that signals are uncertain and preliminary in nature (Uppsala Monitoring Centre, Signals selected by UMC and the clinical review panel: How the process works). This is because, for any given adverse event report considered in generating a signal, there is no certainty that the adverse event was caused by the suspected drug. Rather, the adverse event could have resulted from the underlying condition being treated, a comorbid condition, a concomitant medication, or may simply be the result of chance.

Lilly has completed two reviews of blood dyscrasias including neutropenia which involved assessment of individual case narratives, as well as all available information from other data sources. The first review was conducted in 2006 and covered the period from 26 November 2002 to 26 November 2005, with a second review completed in 2014. As both reviews revealed similar findings and conclusions, we are providing the high level results of the second review as an illustrative example of the evaluations undertaken. Of note, the results of the last review were submitted to the EU Regulatory Agencies in 2014 and no further questions were raised or further actions deemed necessary at that time.

In the second assessment, cases reported between 26 May 2008 and 26 May 2013 and coded to the MedDRA preferred term "neutropenia" were reviewed. Time to onset ranged from approximately 2 months to 11 months, and did not reflect a pattern indicative of a treatment-emergent trend. Thirteen neutropenia cases were identified, but 7 (54%) of those cases either did not provide adequate information to assess the event or presented medical history, historical, or concurrent use of other medication that may provide an alternative explanation for the onset of neutropenia, for example, medical conditions that reduce cell line counts such as human immunodeficiency virus, a family history of autoimmune disorders, or use of medications such as risperidone or valproate. Of the remaining 6 cases, which involved adolescent patients, 5 described neutropenia and 1 neutropenia/leukopenia. Of the 6 patients, 4 patients discontinued atomoxetine treatment while 2 patients continued atomoxetine. Although in 3 of the 4 patients who discontinued atomoxetine the event resolved, these cases did not provide sufficient information, for example, medical history, concomitant medication use, and/or the patient's baseline laboratory values to permit adequate medical assessment. Importantly, without baseline measurements, it is impossible to know whether the condition existed before the patients began taking atomoxetine.

Based on the evaluations summarised above, Lilly has concluded from its previous reviews that there is not sufficient evidence to support a causal association or increased risk between atomoxetine treatment and neutropenia in the treated population. Available information would indicate that the events reported are either incidental findings or may possibly be related to other causes including pre-existing conditions or concomitant medications, as mentioned above, though more information in these cases is needed. In addition, as Dr. Boyd mentioned in his article, no reports of neutropenia in association with atomoxetine could be found in the literature. Case reports and other sources of information that include suspected neutropenia adverse events in atomoxetine-treated patients will be reviewed by Lilly and continue to be monitored through routine pharmacovigilance.

Desloratadine and Aggressive reaction

Lovisa Sandberg, Uppsala Monitoring Centre

Summary

As of March 2015 the WHO Global Individual Case Safety Report (ICSR) database, VigiBase®, included 17 ICSRs of aggressive reaction associated with desloratadine. Desloratadine is a selective peripheral histamine (H1) receptor antagonist, indicated for the relief of symptoms associated with allergic rhinitis and urticaria in children and adults. Ten of the VigiBase reports involved children, of which six presented with a supportive temporal relationship and positive dechallenge, and of those, two reported a subsequent positive rechallenge. The adult reports were less convincing in supporting a signal, but one of the cases represented a rapid onset, positive dechallenge as well as positive rechallenge, and thus this signal is not limited to children. Central nervous system (CNS) adverse reactions have previously been reported for desloratadine, hence penetration into the brain and the possibility of other clinically relevant CNS effects cannot be ruled out. Additional loratadine reports in VigiBase and the fact that aggression is a known adverse reaction for cetirizine, another second-generation antihistamine, contribute to suspicions of a possible class effect.

Introduction

Desloratadine is a non-sedative, selective peripheral histamine (H1) receptor antagonist, indicated for the relief of symptoms associated with allergic rhinitis and urticaria.[1] This second-generation antihistamine was authorized throughout the European Union and the United States in 2001 and is currently available in large parts of the world, including Latin America, Africa and Asia.[1,2,3] Desloratadine is the primary active metabolite of loratadine, a widely used antihistamine which was introduced in 1993 and is now available over the counter.[4,5] Desloratadine is still subject to medical prescription.[1,2]

In the European Union desloratadine is approved for use in adults, adolescents and children over the age of 1 year.[1] In the United States the drug is approved for patients of 6 months and older.[2] The recommended daily dose for adults and adolescents (12 years of age and over) is 5 mg, for children from 6 to 11 years 2.5 mg, from 1 to 5 years 1.25 mg and from 6 to 11 months 1 mg.[1,2] Desloratadine reaches maximum plasma concentration after approximately three hours, and the half-life is about 27 hours. The enzyme responsible for the metabolism is still unknown, so interactions with other medicinal products cannot be excluded.[1]

The most common adverse reactions reported in clinical trials were fatigue, dry mouth and headache (frequency ≥ 1/100 to < 1/10). Additional psychiatric and nervous system adverse reactions reported during the post-marketing period include hallucinations, dizziness, somnolence, insomnia, psychomotor hyperactivity and seizures (frequency < 1/10,000).[1] Aggressive reaction is not listed as an adverse reaction, neither for desloratadine nor loratadine.[1,2,4,5]

Aggression is a wide term and is not a diagnosis in itself. It may instead be a symptom of or related to many different conditions, such as attention-deficit hyperactivity disorder (ADHD) or dementia, and it may overlap with other terms, such as irritability and emotional lability.[6,7] Aggressive behaviour can manifest throughout life and may be part of the natural development process in children. For toddlers and pre-school children aggression generally peaks at 18 to 24 months and slowly decreases by the age of 5.[7] The nature of aggressive behaviour is complex and involves genetic and environmental factors, different neural circuits, and several neurotransmitters, including serotonin (5-HT), dopamine, and GABA.[8]

Reports in VigiBase

As of March 2015 the WHO Global Individual Case Safety Report (ICSR) database, VigiBase®, included 17 ICSRs of the WHO-ART preferred term 'aggressive reaction' associated with desloratadine. The first report entered VigiBase in 2002 and reports have continuously been submitted to VigiBase up to 2014. The majority of the reports (12) originate from Europe (Austria, Croatia, France, Greece, Germany, the Netherlands, Norway, and Sweden), three reports are from the United States, and two from Canada. The cases represent 6 females and 11 males and patient ages range from 1 to 79 years (median age 12 years). The majority of the cases are reported by physicians (7 reports), pharmacists (4), or consumers/non-health professionals (3).

Paediatric reports

Ten of the reports involve children, all but two of them being 8 years of age or younger. The characteristics of these cases are presented in Table 1. All paediatric reports are from 2006 or more recent. Three of the reports were classified as serious by the reporter.

Six of the reports describe that the patient had recovered or was recovering from the reaction at the time

of reporting, all of them upon withdrawal of the drug. Two of the cases describing a positive dechallenge also report a positive rechallenge and one of those describes a repeated positive rechallenge. In the remaining four cases, desloratadine was withdrawn but the patients had not recovered at the time of reporting (3 reports) or the outcome was unknown (1).

Time to onset varies from one or a few days up to seven months. One report does not provide precise time to onset information but the duration of desloratadine use is about one year. For the six reports with positive dechallenge, time to onset is "during administration" (1 report), one to two days (2), three days (2) and a few weeks (1). Desloratadine is the sole suspect drug in all of these six cases; however two of them report concomitant medication previously associated with aggressive behaviour (budesonide) or mood changes (cyamemazine).[5,9] In the latter case, cyamemazine had been used for one year together with risperidone for autism; after adding desloratadine the reaction was experienced two days later. Only one of the remaining

Table 1. Characteristics of paediatric reports of aggressive reaction in association with desloratadine in VigiBase®

Case	Age / Sex	Suspected (S) or concomitant (C) drugs	Reactions*	Time to onset	Dechallenge / Rechallenge	Outcome at time of report	Comment
1	15/M	Desloratadine (S) Risperidone, cyamemazine (both C)	Aggressiveness, behaviour disorder, excitability, titubation	2 days	Positive dechallenge (symptoms began to decline 7 days after withdrawal, however still after 14 days not fully recovered)	Recovering	Daily dose: 1 mg Medical history: Autism Use of concomitant medication for one year
2	8/F	Desloratadine (S)	Aggression, irritability	1-2 days	Positive dechallenge (drug withdrawn after six days, patient recovered within one day)	Recovered	Daily dose: 2.5 mg
3	5/M	Desloratadine (S) Brompheniramine maleate/ pseudoephedrine hydrochloride (C)	Aggression	2 days	Drug withdrawn – outcome unknown	Unknown	Daily dose: 2.5 mg Aggressive behaviour after taking amoxicillin
4	1/F	Desloratadine (S)	Aggressiveness, irritability, nightmare, drug effect lack of	"During administration"	Positive dechallenge Positive rechallenge (repeatedly)	Recovered	Desloratadine taken several times in periods of 5-7 days for about 1.5 years
5	4/M	Desloratadine (S)	Aggression, sleepiness	3 days	Positive dechallenge	Recovered	Daily dose: 2.5 mg One hour time to onset for sleepiness
6	4/M	Desloratadine, clarithromycin, montelukast** (all S)	Aggressive behaviour, stress, fever, petit mal	7 months	Negative dechallenge	Not recovered	Daily dose: 2.5 mg Chlarithromycin treatment stopped two weeks before aggressive behaviour onset
7	12/F	Desloratadine (S)	Aggressive reaction, delirium, psychotic reaction nos, hallucination auditory	5 days	Drug withdrawn and treatment with haloperidol, child's condition has improved	Not recovered	Daily dose: 5 mg
8	8/F	Desloratadine (S) Budesonide**, olopatadine (both C)	Aggressive reaction	"A few weeks"	Positive dechallenge Positive rechallenge (reintroduced with 2.5 mg)	Recovered	Daily dose: 5 mg Daily aggressiveness
9	4/M	Desloratadine (S)	Aggressiveness	3 days	Positive dechallenge (patient recovered within a week after withdrawal)	Recovered	Daily dose: 2.5 mg
10	8/M	Desloratadine (S) Fluticasone**, salbutamol (both C)	Aggressive behaviour, psychic disturbance, insomnia	-	Negative dechallenge	Not recovered	Daily dose: 2.5-5 mg Duration of desloratadine use approximately one year

**Reactions are shown as reported. Due to differences in reporting terminology some terms in the table represent WHO-ART and some MedDRA.*
***Associated with aggressive behaviour.[5]*

four cases reports co-suspected drugs: montelukast, for which aggressive reaction is a labelled adverse reaction, and chlarithromycin, which has been associated with irritability.[5] Chlarithromycin treatment was however stopped about two weeks before reaction onset. Fluticasone, for which aggressive reaction is labelled, is concomitantly used in one case and pseudoephedrine, for which irritability is mentioned as a symptom of overdosage, is concomitantly used in another case.[5]

One report (case 2) describes an 8 year-old female who experienced aggression and irritability following administration of desloratadine for allergic rhinitis, with a latency of one to two days after start of treatment. Desloratadine was withdrawn after six days and the patient recovered within one day. Concomitant medication was not reported and the patient had no known medical history. The past drug therapy indicated that the patient had experienced aggression after a previous intake of a cetirizine tablet and a loratadine tablet on different occasions. The case was reported by a specialist physician and the reaction was assessed as probably related to desloratadine.

Another report (case 4) concerns a 20 month-old female and is reported by the patient's mother. The child was given desloratadine several times in periods of five to seven days for about 1.5 years, mainly for allergic reactions to insect bites. No other medication was reported. The mother described that the child was always rather irritable and aggressive when taking the drug, and at night she seemed to go through something like a nightmare. The sender of the report assessed the reaction as certainly related to desloratadine, because of positive rechallenge.

Adult reports

Seven of the reports concern adults. Two of these present with multiple possible confounders or other more likely reasons for the reaction. For another three adult cases the reported information is sparse, and thus the prerequisites to make proper assessments of these cases are limited. One of them however reports a time to onset of one month.

One case, reported by a specialist doctor, indicates a possible interaction effect from concomitant use of desloratadine and risperidone. The case describes a 38 year-old male who had used desloratadine for years when adding risperidone for autistic disorder. A few hours after the first dose of risperidone the patient experienced violent thoughts, difficulty in standing, dystonia, sedation, trismus and salivation. After withdrawal of risperidone the reactions abated. The patient had previously experienced violent thoughts while on another antipsychotic drug. The reactions may be explained by risperidone alone in this case, however in the light of the paediatric case 1, which also has risperidone co-reported, the interaction hypothesis may also be worth consideration.

The remaining report describes a 32 year-old male presenting with aggressiveness 1-1.5 hours after desloratadine intake. The patient had taken several doses and the reaction is reported to have occurred after each intake. This case also describes a positive dechallenge, with a recovery within 36 hours after drug withdrawal, as well as a positive rechallenge. No concomitant medication was reported. The patient had previously used loratadine and cetirizine without experiencing this reaction.

Literature and Labelling

Psychiatric and nervous system disorder reactions, including hallucinations, dizziness, somnolence, insomnia, psychomotor hyperactivity and seizures, have been reported in association with desloratadine as adverse reactions during the post-marketing period.[1] In three placebo-controlled clinical trials, desloratadine was administered for 15 days to a total of 246 children aged 6 months to 11 years. In infants and toddlers aged 12 months to 23 months emotional lability was reported at a frequency greater than with placebo (3.1%, 0%), as was irritability in infants aged 6 to 11 months (12.1%, 11.3%).[2] Nothing is mentioned in the British National Formulary for Children about the use of desloratadine and adverse events related to aggression.[10] Aggression has been reported as an adverse event in the post-marketing period for cetirizine, another second-generation antihistamine indicated for allergic rhinitis and chronic idiopathic urticaria.[11,12]

First-generation antihistamines have more pronounced sedative properties than second-generation antihistamines, but have also been associated with agitation and irritability.[5,13] These compounds, as compared to second-generation antihistamines, have less H1 receptor selectivity and more easily enter the central nervous system (CNS).[13] It is inconclusive whether the limited penetration of second-generation antihistamines into CNS is determined by active efflux from the brain via P-glycoprotein (P-gp) or a restricted penetration through the blood-brain barrier.[13,14,15]

Cerminara et al. described seizures induced by desloratadine in four children. They speculated that susceptible patients might have a mutation in the gene coding for P-gp, causing an abnormal variant of P-gp, and thus limiting the efflux of desloratadine from the CNS.[16]

Animal studies have indicated that inactivating the histaminergic (H1) system may reduce aggression in rodents, suggestively through decreased serotonin (5-HT) activity.[17,18] However, variations in the histaminergic system and the nature of aggression among species, as well as limitations to animal models[8,19] raise uncertainty to whether these results could be fully applied to humans.

Discussion

VigiBase paediatric reports on aggressive reaction and desloratadine represent six cases with a supportive temporal relationship and positive dechallenge, and of these, two reported a subsequent positive rechallenge. Four of these cases had no other medication reported while one case reported concomitant use of another antihistamine (eye drops) and a corticosteroid (nasal spray) previously associated with aggression, and another case reported concomitant use over a period of one year of antipsychotic drugs indicated for autism.

Two additional paediatric cases reported a time to onset consistent with the other cases, but negative or unknown outcome of dechallenge. One of these cases however reported that the patient was improving upon withdrawal of the drug together with treatment of haloperidol. This case described other reactions, including psychotic reaction and hallucinations, the latter a known adverse reaction for desloratadine and which may lead to aggression.

The remaining two cases involving children were less convincing with long or missing time to onset, negative dechallenge and co-reported drugs previously associated with aggression.

The medical histories of the patients were seldom reported and identified possible confounders were few in relation to the number of paediatric reports. The neurological and behavioural development of children may be seen as a confounding factor and differentiating coincidental aggressiveness as a natural course of development, from a true causal association is difficult. However, a possible causal relationship is supported by a plausible temporal relationship, positive de- and rechallenge, and complementary adult cases.

The adult reports were less convincing in supporting a signal. However, one of the adult cases presented no obvious confounders, a rapid onset of the reaction, positive dechallenge as well as positive rechallenge, and thus this signal is not limited to children.

The main proportion of the cases did not indicate a serious reaction; however, aggression may have severe implications. As aggressive behaviour sometimes involves violence, both the patient him/herself and his/her surroundings may be at risk of being physically injured, and aggressive behaviour, even if only verbal, may have consequences on social interactions and the quality of life. Another implication is the legal aspect, in which it may be important to find explanations for aggressive action.

Although desloratadine is said not to readily cross the blood-brain barrier, this cannot be completely excluded and there have been reports of CNS adverse reactions from this drug.[1,2,16] One example is emotional lability, which may in a wider sense include the term discussed in this signal, found to be reported at greater frequency for desloratadine than for placebo in infants and toddlers.[2] The neurobiology of aggression is complex and is supposed to involve many different neural circuits and neurotransmitters and a mechanism can only be speculated. However, penetration into the brain and the possibility of triggering clinically relevant CNS adverse effects in susceptible patients, cannot be ruled out. Worth noting is that half of the paediatric cases had a higher than recommended daily dose, indicating a possible dose-relationship. Two of these cases also reported concomitant use of another antihistamine, which may suggest a possible additive effect.

The range of countries reporting this association strengthens the signal in the sense of being broadly observed. Also important to highlight, when this combination was assessed, VigiBase contained in addition 108 reports (45 paediatric) of an aggressive reaction associated with loratadine, entered between 1992 and 2015 and originating from 13 different countries. This, together with the fact that aggression is described as an adverse reaction for cetirizine[11,12], another second-generation antihistamine, points to a possible class effect.

Conclusion

Reports in VigiBase primarily, but not exclusively, support a signal on aggressive reaction associated with desloratadine use in children. The paediatric reports represent a plausible temporal relationship, positive de- and rechallenges and only a few identified possible confounders. Psychiatric and neurologic adverse reactions have been reported for the drug and thus penetration into the brain and the possibility of other clinically relevant CNS effects cannot be excluded. Additional loratadine reports in VigiBase and the fact that aggression is a known adverse reaction for cetirizine, contribute to suspicions of a possible class effect.

Thank you to the national pharmacovigilance centres contributing additional case information upon request.

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Dextromethorphan and Serious neurological disorders in children

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In the screening of paediatric individual case safety reports (ICSRs) from the WHO Global ICSR database, VigiBase® the adverse drug reaction (ADR) ataxia was highlighted for the drug dextromethorphan. The substance is used in many cough, cold and flu products sold over the counter globally. It is approved for children and adults above 6 years of age in the United Kingdom and above 4 years of age in the United States.[1,2] Most dextromethorphan containing products in the United Kingdom are however indicated from the age of 12.[1]

Widening the search in VigiBase to include reports on the whole WHO-ART System Organ Class (SOC) Neurological disorders revealed several serious ADRs. As of February 2015 there were 110 reports for children under the age of 6 years for the whole SOC. The reports originate from Asia, Europe, Latin and North America. Among the reported terms were ataxia, convulsions, dyskinesia and coma. There were 29 reports for the WHO-ART High Level Term (HLT) ataxia and 10 reports for the HLT coma (all reports of coma were for children of 2 years of age or less). For all children (younger than 18 years) there were 51 reports for the HLT ataxia, and 19 reports with the HLT coma. In the summary of product characteristics (SPC) for several products containing multiple ingredients including dextromethorphan, coma is listed in the section for overdoses but for drugs containing *only* dextromethorphan in the United Kingdom, coma is not listed as a possible ADR other than as a contraindication in patients using MAO-inhibitors.[1] In 2008/2009 the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM) in the United Kingdom advised that children under 6 years should not be given over-the-counter cough and cold medicines containing dextromethorphan.[3]

Nonetheless, reports on dextromethorphan associated with serious ADRs within the SOC Neurological disorders for children below the age of 6 have continued to be reported to VigiBase after 2009 (the latest submitted in 2014). The majority of these reports are not co-reported with accidental intake of the drug or overdose. Continuous reporting of serious neurological ADRs associated with off-label use of dextromethorphan in young children suggests that the risk-benefit balance for dextromethorphan is not clear to parents. Further revisions of the patient information leaflets are advised to clearly highlight the risk of serious neurological reactions in young children.

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HPV vaccine and Gastrointestinal motility disorders

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Summary

Gastrointestinal motility disorders have been identified in association with the human papilloma virus vaccine as a potential signal from the WHO Global Individual Case Safety Report database, VigiBase®. Using the WHO-ART preferred terms of gastric dilatation and bowel motility disorder, twenty one unique cases are included in the signal with a majority of cases co-reporting the symptoms of abdominal pain, nausea and/or vomiting. It has been increasingly recognised that autonomic neuropathies can cause gastrointestinal motility disorders by involvement of the enteric nervous system. Human papilloma vaccines have recently been reported in association with two signals describing autonomic nervous system dysfunction, one arising in Japan in the form of complex regional pain syndrome (CRPS) and another in Denmark and the US in the form of postural orthostatic tachycardia syndrome (POTS). Comparison of the symptomatology described in the cases of gastrointestional dysmotility, CRPS, and POTS reveal a certain amount of overlap, leading to speculation that there could be an association between human papilloma virus vaccination and autonomic nervous system dysfunction. It is acknowledged that there are uncertainties regarding exact pathophysiologic mechanisms as well as reliable data on background incidence of autonomic neuropathies in the target population; however, the potential for a common pathology in three separately identified signals warrants attention.

Introduction

There are two human papilloma virus vaccines currently available for use for the prevention of premalignant genital and anal lesions, cervical and anal cancers causally related to certain oncogenic human papillomavirus (HPV) types, as well as genital warts (condyloma acuminata) causally related to specific HPV types. There are two HPV vaccines currently on the market, a quadrivalent vaccine which protects against HPV types 6, 11, 16, and 18 and a bivalent vaccine which protects against HPV types 16 and 18.

Gastric dilatation is a WHO-ART preferred term (PT) which encompasses the included terms (IT) of impaired gastric emptying, gastric atony, gastroparesis, gastric dilatation, and stomach dilatation. Bowel motility disorder is a WHO-ART PT which includes only the IT bowel motility disorder.

The most common gastrointestinal motility disorders in children are gastroesophageal reflux disease (GERD), esophageal achalasia, gastroparesis, chronic intestinal pseudoobstruction, and constipation. Gastroparesis and chronic intestinal pseudoobstruction are considered to be relatively poorly characterized in the pediatric population.[1]

Gastroparesis is defined as a gastric motility disorder which is characterized by delayed gastric emptying in the absence of mechanical obstruction.[1] Symptoms of gastroparesis typically include vomiting (68%), abdominal pain (51%), nausea (28%), weight loss (27%), early satiety (25%), and post-prandial fullness (7%).[2]

There are no data available on the prevalence of gastroparesis in the pediatric population; however, the age-adjusted prevalence in adults has been estimated to be 9.6 per 100,000 for men and 37.8 per 100,000 for women.[3] There have been two respective reviews of gastroparesis in children, including around 230 children in each of the two cohorts.[2,4] There is an increased male to female incidence in infancy, an equal ratio in children, and an increased female to male incidence in adolescence. The majority of the cases in one cohort were considered to be idiopathic (70%), drug-induced (18%), and post-surgical (12.5%); the other cohort reported post viral gastroparesis in 18% and mitochondrial dysfunction in 8%. Drugs which can result in delayed gastric emptying include alpha-2 adrengeric agents, tricyclic antidepressants, proton pump inhibitors, H2 receptor agonists, antacids, calcium channel blockers, as well as narcotic agents.[5-11] Chronic intestinal pseudo-obstruction (CIPO), a rare disorder, is characterized by severe, recurrent or continuous, symptoms including abdominal distension, vomiting and abdominal pain. There are radiographic signs of dilated bowel with air-fluid levels without evidence of obstructing lesions. Primary CIPO can be neuropathic, myopathic or idiopathic and is typically diagnosed within the first year of life. Secondary CIPO can be associated with a variety of systemic disorders, including metabolic disorders, mitochondrial myopathies, connective tissue diseases, endocrinopathies, and diseases of the nervous system. Most children with CIPO require some form of nutritional support, and the overall mortality rate has been reported to be between 10-32%.[1]

Reports in VigiBase

Twenty-one individual case safety reports (ICSRs) describing gastrointestinal motility disorders using the WHO-ART preferred terms of "gastric dilatation" and "bowel motility disorder" in association with human papilloma vaccines were identified in the WHO Global ICSR database, VigiBase®, up to 1 April 2015. All cases were female with ages ranging from 11 to 26 years. There are two reports without information on age provided.

Seventeen cases report gastrointestinal motility disorders with Gardasil and four cases report events with Cervarix.

Time to onset was reported for 18 cases and ranged from one day to two years with a median value of 8-13 days, depending on which starting day is considered. Eleven cases provided information on time to onset in relation to the number of the dose: seven reported symptoms after dose one and ranged from one day to six months (cases 2, 3, 9, 12, 14, 15, 17) with a median of 60 days; seven reported symptoms after dose two and ranged from one day to three months (cases 3, 5, 8, 9, 12, 14, 17) with a median value of 19 days; two reported symptoms after dose three (case 1 and 18, respectively 15 months and 1 day).

The first eight cases in the Table 1 below report abdominal dysmotility, with either co-reported terms or additional information from the narrative, which are suggestive of autonomic neuropathy/dysfunction.

Case 1 was considered an index case. It concerns a 17 year-old woman without significant past medical history and a stable family background. She was vaccinated with Gardasil on three occasions within six months. The subject was hospitalized 15 months after the last dose with increasing abdominal pain, nausea and vomiting. She was referred to the gastrointestinal service 3.5 years later for continuing abdominal pain of unclear origin and a weight loss of 22 kg. She underwent an extensive evaluation including a gastric emptying study, stationary antroduodenojejunal manometry, SmartPill test with blood sampling. All studies revealed evidence of decreased motility. In addition, numerous studies including laparoscopic surgery excluded lesions or masses as a cause of intestinal obstruction. A small bowel transmural biopsy was performed at two levels. Histopathology showed neuronal damage of the plexus myentericus consistent with ganglionitis. She was diagnosed with chronic intestinal pseudoobstruction and gastroparesis. At the time of the reporting of the adverse event, daily painful abdominal pain attacks, little relieved by analgesics, were continuing. Food intake was nearly impossible and parenteral nutrition was demanded.

The next six cases (cases 2 to 7) co-report terms such as palpitations, headache, dizziness, presyncope, vertigo, fatigue, malaise as well as postural orthostatic tachycardia syndrome. Case 2 co-reports, as concomitant, Claritin (loratadine) a drug that is known to cause tachycardia and palpitations. Case 8 co-reports terms which are suggestive of a pan-dysautonomia including neurogenic bladder and visual impairment without evidence of a clear lesion on neurologic, neuroradiographic and neurophysiologic evaluation.

The next four cases (cases 9 to 12) in the table report only symptoms related to gastrointestinal dysmotility.

The remaining nine cases (cases 13 to 21) report additional terms suggestive of a cause of the gastrointestinal motility disorder; many of these diagnoses have themselves been associated with autonomic neuropathies. Peripheral neuropathy, Crohn's disease, scleroderma/polymyositis/interstitial lung disease/ANA factor test positive; colitis ulcerative, postural orthostatic tachycardia syndrome/Guillian-Barre Syndrome/multiple sclerosis; colitis/ileitis/Crohn's disease; history of congenital lack of rotation of intestines; colitis ulcerative/tranverse myelitis; transverse myelitis; and demyelination/multiple sclerosis. It is worth noting that most of these cases also co-report terms which are suggestive of the autonomic neuropathy: malaise, headache, fatigue, dizziness.

Outcome information was provided for seven cases: one reported outcome as recovered (case 12); six reported outcome as not recovered (cases 1, 3, 5, 6, 8, 19). Two case narratives provide information suggestive of the severity of the event: case 6 reported the placement of a pacemaker into the stomach, case 9 reports gastrointestinal tube insertion and case 11 reports that six weeks of school were missed. Similar such details have been reported for patients with suspected autonomic neuropathy (cases 1 and 5).

Finally, there are two cases which provide information on rechallenge: case 12 includes the co-reported MedDRA term, "vaccine positive rechallenge" and case 15 reports in the case narrative that the subject has increasing abdominal pain with subsequent doses of the vaccine.

Table 1. Cases of gastrointestinal motility disorders in association with human papilloma virus vaccine in VigiBase®

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Time to onset	Reported terms (WHO-ART)	Outcome/Comments
1	17/F	Gardasil (S)	15 months after dose 3	Gastroparesis, gastric atony	Not recovered
2	16/F	Gardasil (S), Claritin (C)	2 weeks after dose 1	Impaired gastric emptying, abdominal pain, diarrhoea, oral intake reduced, weight decreased, palpitations, appetite decreased	-
3	12/F	Gardasil (S)	1 month after dose 1; 1 day after dose 2	Bowel motility disorder, abdominal pain, nausea, bloating, headache, dizziness, palpitations, anxiety	Not recovered
4	21/F	Cervarix (S)	4 years for chronic fatigue syndrome and POTS	Impaired gastric emptying, abdominal pain upper, nausea, vomiting, vertigo, presyncope, tachycardia, autonomic nervous system imbalance, chronic fatigue syndrome, postural orthostatic tachycardia syndrome*	-
5	12/F	Cervarix (S)	1 week after dose 2	Gastric atony , bowel motility disorder, abdominal discomfort, abdominal pain, aphagia, constipation, fatigue, gastroesophageal reflux	Not recovered Diagnosed with post viral dysmotility. Eating difficult secondary to gastric discomfort. Severe fatigue.
6	17/F	Gardasil (S)	173 days	Impaired gastric emptying, vomiting, abdominal pain, malaise, depression	Not recovered Required pacemaker placement in stomach. Daily activities impaired.
7	17/F	Cervarix (S)	Less than 2 days	Bowel motility disorder, abdominal pain, headache aggravated, fatigue, lymphadenopathy, influenza-like symptoms, gastrointestinal infection	Neither causal association with Cervarix nor gastrointestinal infection could be excluded.
8	11/F	Gardasil (S)	19 days after dose 2	Bowel motility disorder, bladder neurogenic, confusional state, incoherent speech, visual impairment	Not recovered Neurologic, neuroradiologic, neurophysiologic evaluations without abnormality.
9	11/F	Gardasil (S)	60 days after dose 1; within 1-2 weeks of dose 2	Impaired gastric emptying	Gastrointestinal tube insertion. Hospitalised for 2 weeks.
10	-/F	Gardasil (S)	-	Impaired gastric emptying	-
11	11/F	Gardasil, Boostrix, Havrix, Varivax, Fluzone (all S)	1 day	Impaired gastric emptying, abdominal pain, nausea, vomiting	Daily activities impaired and Hospitalised for seven days.
12	14/F	Gardasil (S)	6-7 months after dose 1; 26 days after dose 2	Impaired gastric emptying, diarrhoea, vomiting, vaccine positive rechallenge*	Recovered
13	26/F	Gardasil (S)	-	Impaired gastric emptying, abdominal distention, abdominal pain, coeliac disease, anxiety, convulsions, dizziness, dyspareunia, fatigue, gait disturbance, headache, hemiparesis, hemiplegia, hypoasethesia, menorrhagia, neuropathy peripheral, pelvic pain, photophobia	-
14	14/F	Gardasil (S)	3 months after dose 1; within same month of dose 2	Gastric atony, abdominal pain upper, arthralgia, myalgia, ANA factor test positive, interstitial lung disease, polymyositis, scleroderma	Dysfunction of esophagus, suspicious of intestinal pseudo-obstruction. ANA positive with anti-PM/Scl pattern.
15	-/F	Cervarix (S)	1 day after dose 1	Gastric dilatation, abdominal distension, abdominal pain upper, colitis ulcerative, gastritis, gastroesophageal reflux, haematemesis, haematochezia, malaise	Patient history reports increasing abdominal pain with subsequent doses of vaccine. Received three doses.
16	21/F	Gardasil (S)	9 days	Impaired gastric emptying, nerve damage, tachycardia, postural orthostatic tachycardia syndrome*, convulsions, Guillain-Barré syndrome, multiple sclerosis, vision blurred, diplopia, fatigue, headache, arthralgia	-
17	14/F	Gardasil (S)	146 days after dose 1; 91 days after dose 2	Impaired gastric emptying, abdominal pain, anorexia, asthma, chest pain, colitis, Crohn's disease, dizziness, eosinophila, ileitis, malaise, nausea, oesophagitis, vomiting, weight decrease	Gastrointestinal tube insertion
18	24/F	Gardasil (S)	1 day after dose 3	Gastric atony, abdominal pain, abdominal tenderness, amylase increased, creatinine blood increased, urea blood level increased, deep vein thrombosis, malaise, migraine, nausea, pancreatitis, photophobia, sinus bradycardia, visual impairment	History of congenital lack of rotation of intestines. Transplant of intestines, pancreas, stomach and liver.
19	26/F	Gardasil (S)	2 years	Bowel motility disorder, abdominal pain upper, haematochezia, colitis ulcerative, sensory disturbance, paralysis, transverse myelitis	Not recovered. Diagnosed with ulcerative colitis, transverse myelitis.
20	11/F	Gardasil, Boostrix, hepatitis A vaccine**, meningococcal vaccine **(all S)	4 days	Bowel motility disorder, bladder neurogenic, muscle weakness, sensory loss, transverse myelitis	Diagnosed with transverse myelitis by MRI.
21	27/F	Gardasil (S)	11 days	Bowel motility disorder, muscle weakness, demyelination, multiple sclerosis	Diagnosed with multiple sclerosis.

**MedDRA terms ** Product name not specified*

Literature and Labelling

Included in the labelling for Gardasil are nausea (common) and vomiting (not known). Included in the labelling for the Cervarix are "gastrointestinal symptoms" included nausea, vomiting, diarrhea, and/or abdominal pain. In addition, it is noted that the terms of Guillain-Barrè Syndrome is included in both the US and EMA labelling and transverse myelitis is included in the US label.[10,11,12,13]

It is becoming increasingly recognized that a subset of gastrointestinal motility disorders are caused by autonomic neuropathies which involve the extrinsic nerves of the gut.[14,15] A study of eight children, aged ten to seventeen, with recurrent abdominal pain were tested for autonomic nervous system abnormalities. Results were abnormal in seven patients: sympathetic function was reduced in cardiac (reduced tachycardia in phase II of Valsalva), vasomotor (postural tachycardia) and sudomotor (reduced sweating) systems; parasympathetic function was normal in all patients. The authors hypothesize that the most likely explanation is a constitutional reduction in sympathetic overflow.[16]

Human papilloma vaccines have recently been reported in association with dysfunction of the autonomic nervous system in a number of publications. First, a signal of complex regional pain syndrome arose in Japan in the summer of 2013. Kinoshita et al. have described the symptomatology of 40 girls, aged 11 to 17 years, who were diagnosed with peripheral sympathetic nerve dysfunction after receipt of HPV vaccination. The most common symptoms were headaches (70%), fatigue (53%); and coldness of the legs (53%). Eighteen of the girls were diagnosed with complex regional pain syndrome (CRPS) type I (reflex sympathetic dystrophy). Four patients were diagnosed with postural orthostatic tachycardia syndrome and eight with orthostatic hypotension (OH). Two patients with CRPS and concomitant OH or POTS had evidence of post-ganglionic sympathetic neuropathy as evidenced by decreased plasma levels of noradrenalin, abnormal MIBG cardiac scintagram findings, and an ultrastructural pathology of intradermal unmyelinated nerve fiber degeneration. The authors speculate that, based on the temporal relationship between immunization and the development of symptoms (average time to onset, 5.47 months +/- 5 months), they cannot exclude the possibility that immunization with HPV vaccines may secondarily induce sympathetically mediated disorders.[17]

Second, a signal of postural orthostatic tachycardia syndrome arose in Denmark in the autumn of 2013. Brinth et al. have described the suspected side effects of HPV vaccine in 53 females, aged 12 to 39 years, who reported symptoms within two months of vaccination. The most common symptoms were headache (100%), orthostatic intolerance (96%), and fatigue (96%). Ninety-one percent of subjects reported nausea, 77% reported feeling bloated, 70% reported abdominal pain. Sixty-six percent of subjects reported neuropathic pain. Approximately half of these patients met criteria for a diagnosis of POTS. The authors suggest that the pathogenic alteration in their patients is located in the autonomic nervous system and that further research is urgently warranted to further clarify the pathophysiology and evaluate a possible causal association with HPV vaccine.[18,19] This signal has, in fact, been independently described in a case series including six patients reported from the US.[20]

Finally, it is notable that there is a form of autoimmune autonomic neuropathy (AAN) which has been described. It is an antibody-mediated neurological disorder in which patients typically present with the rapid onset of severe autonomic failure manifested as orthostatic hypotension, gastrointestinal dysmotility, anhidrosis, bladder dysfunction, sicca syndrome, and impaired papillary light reflex. AAN is mediated through antibodies to nicotinic acetylcholine receptors (AChR) located in sympathetic, parasympathetic, and enteric ganglia.[21] AAN typically presents in previously healthy, young or middle-aged individuals and in its usual course results in a clinical picture that reaches a peak severity within a few days to weeks. The course may be monophasic with spontaneous recovery, while other patients may have a more chronic and progressive course. Motor and sensory nerve conduction studies are normal. Symptoms include orthostatic hypotension, anhidrosis, as well as urinary retention, dry mouth, impaired papillary light response, gastrointestinal dysmotility is common and manifests as postprandial abdominal pain, early satiey, vomiting or intestinal pseudo-obstruction.[22]

Other phenotypes of AAN, including idiopathic gastrointestinal dysmotility and postural orthostatic tachycardia syndrome, have been recognized with the availability of testing for autoantibodies to ganglionic AChR. Antibodies that bind to the gangionlic AChR are detectable in about 50% of patients with subacute AAG and to a less extent in subjects with POTS (10-15%) and idiopathic gastrointestinal dysmotility (5-10%).[21]

Although human papilloma vaccines specifically have not been linked to AAN, it is noteworthy they have now been linked to gastrointestinal dysmotility and POTS which are both milder phenotypes of this type of autonomic dysfunction.

Discussion and Conclusion

The signal for human papilloma virus vaccine and gastrointestinal dysmotility consists of 21 ICSRs which were identified in VigiBase. Ten of the cases report terms or have narrative information which describe similar symptomatology (palpitations/tachycardia, vertigo/presyncope, fatigue, and headache) and suggests the possibility of an underlying pathology consistent with autonomic nervous system dysfunction. Given the recognition of autonomic neuropathy as a cause of gastrointestinal motility disorders as well as the recent reports of two cohorts of HPV vaccine populations suffering from autonomic nervous system dysfunction in Japan and Denmark, it appears possible to consider a causal relationship between HPV vaccination and autonomic dysfunction which may manifest in the form of dysautonomia, gastrointestinal dysmotility, POTS, and/or CRPS type I.

Almost half of the remaining cases co-report additional terms which could explain the cause for gastrointestinal dysmotility. Of note, many of the reported terms are themselves associated with autonomic dysfunction: multiple sclerosis and transverse myelitis for example.

It is acknowledged that the exact site of potential injury is not clear based upon the current data; neither is the exact nature of the pathology, whether inflammatory or autoimmune or other unknown mechanism. In those cases with explanatory diagnoses, sites of injury are suggested (multiple sclerosis, transverse myelitis); however, the case narrative included in the signal reported biopsy findings which were consistent with ganglionitis.

Further complicating this signal are the relatively scarce data on the prevalence of the various types and subtypes of autonomic dysfunction in the pediatric population as well as an increasing awareness and thus diagnosis of these types of disorders in the segment of the population which routinely receives the human papilloma vaccine. Also lacking at the current time is a known biological mechanism by which the human papilloma vaccine would cause pathology to the autonomic nervous system, although an autoimmune pathophysiology in predisposed individuals could be considered as was recently exemplified in the Pandemrix-narcolepsy.[23]

In spite of the limitations of this signal at the present time, given that autonomic dysfunction has potentially manifested as three separate phenotypes, oftentimes overlapping, in three separate signals from three separate institutions, it appears that action is warranted, such as preclinical studies, patient registries and/or other post authorisation safety measures. Furthermore, given the recent licensure of the new human papilloma virus vaccine; Gardasil 9 which contains increased amounts of antigen as well as adjuvant relative to quadrivalent Gardasil, which contributes to this signal, this potential safety concern requires attention.

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Response from GSK

Following this request, GSK performed analysis of gastrointestinal motility disorders after vaccination with Cervarix using MedDRA Preferred Terms (PTs) 'Gastric atony', 'Gastric dilatation', 'Impaired gastric emptying' and 'Gastrointestinal motility disorder" that matches the WHO-ART terms used in analysis conducted by the WHO.

Results: The pooled safety analysis of clinical trial data that evaluated 57,580 subjects did not identify any imbalance between study groups for the 4 selected MedDRA PTs and Gastrointestinal System Organ Class in general (Angelo, 2014). This analysis provided no statistical evidence for an increased risk of any autoimmune disease after Cervarix vaccination compared to controls.

Globally, only two spontaneous cases were reported from UK following over 55 million distributed worldwide as follows:

- A non-serious case concerns a 13-year old female that reported gastroparesis with time to onset (TTO) of 1 month after 1st dose that was considered as a post infectious gastroparesis that resolved after unspecified time. Company Comment: Based on the reported information, relationship can be assessed as inconsistent with causal association to vaccination, according to the WHO criteria (2013).

- A serious case reported for a 21 year-old subject who experienced an episode of extreme dizziness within 2 days after dose 1 and that re-occurred and persist after dose 2. On an unknown date after vaccination with the 2nd dose, she was diagnosed with autoimmune encephalitis, POTS, chronic fatigue syndrome (CSF) and epilepsy. Symptoms such as bloating, loss of appetite, nausea, stomach pain and impaired gastric emptying with unknown TTO were reported but lack details. As low carbohydrates (FODMAP) diet was recommended, Irritable bowel syndrome can not be excluded. Company Comment: several co-reported diagnoses, such as Autonomic nervous system imbalance, POTS, NDMA encephalitis and epilepsy makes it impossible to evaluate causality. Case can be assessed as indeterminate by WHO criteria, 2013.

The data presented in these cases is inconclusive and does not represent a signal at this stage. However, given the potential association between HPV vaccination and autonomic disorders, the Company considers that these events require further monitoring through routine pharmacovigilance.

As gastrointestinal motility disorders is suggested to be associated with autonomic neuropathy, GSK has additionally looked at case reports that included the MedDRA PTs of 'Autonomic nervous system imbalance', 'Autonomic neuropathy', 'Autonomic failure syndrome', 'Autonomic dysreflexia', 'Autonomic nervous system neuropathy' and 'Autoimmune neuropathy'(DLP: 20 April 2015). A total of 16 cases were retrieved (reporting rate: 0.03 cases per 100,000 doses distributed). Subjects age range was 12 -20 years with median 13 years. No cases were identified with MedDRA PTs 'Autonomic nervous system neuropathy' and 'Autoimmune neuropathy. The majority of the cases (11) were reported from Japan, followed by United Kingdom (4) and Latvia (1). TTO varied from 0 days up to 1 year after vaccination with the 3rd dose. Two cases were poorly documented, 4 cases reported symptoms suggestive for psychogenic reactions in the form of syncope, one case provided an alternative cause (pneumonia mycoplasmal) and TTO for one case was too long (1 year after 3rd dose) for a causal association. For the remaining 7 cases, reported data is insufficient to confirm the diagnosis of autonomic neuropathy and hence causal relationship could be assessed as indeterminate. Overall, no consistent pattern of TTO and conditions were identified in these cases.

As part of the routine signal detection process, the company employs a signal detection tool based on a quantitative signal of disproportionate reporting for a vaccine-event pair which is stratified by sex, age groups, regions and calendar time periods. No quantitative signal was observed for any MedDRA PT included in this review.

In the WHO signal document, CRPS was suggested as one of the possible forms of autonomic nervous system dysfunction, as described by Kinoshita et al (2014) which presents Japanese cases of CRPS following Cervarix or Gardasil. This paper described peripheral sympathetic nerve dysfunction in 40 adolescent Japanese girls following immunization with any HPV vaccine. According to the authors, 4 girls fulfilled the Japanese clinical diagnostic criteria of CRPS and 14 the Harden Bruehl criteria (Harden RN, 2007). The paper describes 5 representative case reports. However, based on description of cases, none fulfilled the criteria to confirm the diagnosis of CRPS. The authors

also described a postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension (OH) and low plasma levels of noradrenaline in some of the patients and claimed that this confirms the diagnosis of CRPS. Whereas low plasma levels of noradrenaline are described in CRPS, POTS and OH are not general findings in CRPS. Moreover the sympathetic dysfunction is typically local and distal in one of the extremities and in no way general (Wasner, 2010), as seems to be the case with the girls described in the article.

Following different analyses conducted by GSK and other external review bodies (e.g.WHO, 2013, EMAPRAC, 2013, UKMHRA, 2012, PEI Germany, 2013) with regard to CRPS, causality to HPV vaccination has not been established. Given this inconclusive outcomes and as recommended by the PRAC, CRPS will continue to be closely monitored via routine pharmacovigilance including the development of a targeted follow-up questionnaire to ensure complete documentation of suspected cases and allow a robust data evaluation/validation.

At this stage, no signal was observed for POTS following Cervarix vaccination.

The review of data currently available to GSK do not suggest an increased risk of autoimmune diseases following vaccination with Cervarix (Angelo, 2014a, Angelo, 2014b)

Altogether given the number and nature of case reports that have been identified for Cervarix, the currently available data on gastrointestinal motility disorders is inconclusive and does not represent a signal. Causality between CRPS, POTS and HPV-vaccination has not been established to date. Given the insufficient data on hand, the company will further monitor these events via routine pharmacovigilance.

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Response from MSD

Background

Twenty-one individual case reports describing gastrointestinal motility disorders using the WHO-ART preferred terms of "gastric dilatation" and "bowel motility disorder" in association with human papilloma vaccines were identified in the WHO Global Individual Case Safety Report (ICSR), VigiBase, and were assessed as constituting a potential signal. Of these case reports, 17 were identified for the quadrivalent vaccine protecting against HPV types 6, 11, 16, and 18, Gardasil, and 4 case reports were identified for the bivalent vaccine protecting against HPV types 16 and 18, Cervarix. All cases were female with ages ranging from 11 to 26 years (age unknown in 2 reports).

Discussion

The analysis of the time to onset with a range from 1 day to 2 years does not reveal a clear pattern. Also the gastrointestinal events, representing symptoms and diagnosis, reported for the 21 patients do not represent a consistent pattern nor do they suggest a common cause. Specifically the case report presented as the pivotal case (case 1), suggests other triggers based on a lag time of more than a year after the third vaccination. Although in 2 cases a positive rechallenge was reported, it was apparently not specified which event(s) reoccurred, and the reported increasing abdominal pain with subsequent doses of the vaccine in 15 reports could reflect psychosomatic reactions. With approximately 178 million doses distributed the rate of these case reports is very low. Abdominal pain is a common event in the target population for this vaccination, and the described symptoms and/or diagnoses of gastric disorders appear consistent with what would be expected in the general population. While gastrointestinal motility disorders in children and adolescents are considered common, they are challenging to diagnose and have no standard case definition (1-4). No prevalence estimates and limited epidemiologic data for gastroparesis are available for pediatric populations. A cohort study in Minnesota (United States) reported the incidence (per 100,000 person-years) in females aged 10-30 with "definite or probable gastroparesis" as ~5-10, and ~5-15 when cases of "possible gastroparesis" were included, with higher rates in older ages (5). Among adolescents, the primary symptoms are nausea and abdominal pain, with a predominance of female cases (3,6). In 2 large pediatric studies, up to 70% of patients had idiopathic gastroparesis and comorbidities were common (3,6) Autonomic dysfunction can be associated with gastroparesis, and these cases tend to have rapid gastric emptying (7). The authors acknowledge that the pathophysiologic mechanisms underlying gastrointestinal motility disorders in children and adolescents are poorly understood. But although no clear time to onset and no evident symptomatology pattern can be demonstrated, the authors claim that the described cases could be seen in the realm of a proposed association of human papilloma vaccines with symptoms of dysfunction of the autonomic nervous system like complex regional pain syndrome (CRPS) or orthostatic tachycardia syndrome (POTS). It is commonly acknowledged that CRPS is often associated with minor trauma inciting the event. Post immunization CRPS in the pediatric population has been reported following rubella and hepatitis B immunization. Richards et al. (10) propose that the IM injection itself is the stimulus that triggers the development of CRPS pain and not the contents of the vaccine, citing other needle-based interventions such as venipuncture and IV drug administration preceding CRPS. The reporting rate of CRPS post vaccination with Gardasil is very low given the large number of doses distributed. Regarding the speculation of a vaccination induction of POTS it has to be pointed out that this syndrome involving orthostatic intolerance is generally not well understood and that its subtypes further complicate diagnosis and treatment of the individual patient. Based on the Gardasil MAH's evaluation of case reports, there is no evidence, that the vaccine is causally related to any of the events of POTS; they appear only temporally related, the reporting rate is very low, and they may represent the background incidence for this condition. A local cluster of reports originating from Denmark reflects a special situation without established causal association with the vaccination. The MAH for Gardasil agrees with the authors that some of the case reports presented could reflect autonomic neuropathy/dysfunction, specifically reports including palpitations, tachycardia, vertigo, presyncope, fatigue, and headache, but in none of the case reports a causal association to the vaccination can be established. A review of the Gardasil MAH's data does not reveal a safety signal for gastrointestinal motility disorders. As noted by the authors, the labelling for Gardasil adequately includes nausea and vomiting as adverse reactions. At this point, apart from routine pharmacovigilance, no additional safety measures are warranted.

Conclusion

Close to 10 years of experience with Gardasil with greater than 178 million doses distributed

and several large, observational safety studies performed in Europe and USA show no correlation between GI events and vaccination (8-9). Regarding the alleged association of dysfunctions of the autonomous nervous system and the vaccination no connection between CRPS and/or POTS can be established. These are separate and different entities occurring in the target population. With high background rates of events related to GI motility disorders (1-5) as published by several investigators, the reported very small number of events, in relation to the high number of doses of Gardasil distributed worldwide, most probably reflects the background incidence of these conditions in the target population. In general, the author's case report evaluation has to be seen in the light of limitations associated with spontaneous adverse event reporting including the insufficient information provided, variable data quality, and especially the missing information on diagnostic measures. Taking everything into account, the authors offer no solid scientific evidence for a possible adverse reaction but speculations that are based on a very small number of spontaneous reports. Neither the Gardasil MAH's postmarketing nor clinical data, nor published observational safety studies, suggest a safety signal for the described gastrointestinal motility disorders. The MAH will continue to monitor cases of gastrointestinal motility disorders as reported in temporal association with Gardasil. The MAH's ongoing review of the safety profile of Gardasil continues to support its positive Benefit- Risk profile.

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Olanzapine and Accidental drug intake by children

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In the screening of paediatric individual case safety reports (ICSRs) from the WHO Global ICSR database, VigiBase® the adverse drug reaction (ADR) miosis was highlighted for the drug olanzapine in young children. Olanzapine is not indicated for children and adolescents due to lack of data on safety and efficacy.[1] As of March 2015 there were eight reports of miosis for children below the age of 6 years. The signs of miosis reflect the anticholinergic properties of olanzapine. An assessment of the reports revealed that the WHO-ART preferred terms (PT) accidental drug intake by child, accidental overdose, or medication error was co-reported in six out of the eight reports. Widening the search to the WHO-ART high level term (HLT) medication error related problems revealed 20 reports for olanzapine within the age group excluding two suspected duplicates. More than half of those reports represented accidental drug intake (by child, accidental exposure to product or accidental overdose). The reports originated from Asia, Europe, North America and Oceania.

Accidental overdose with olanzapine in children is well described in the literature, including several published case reports (of which a few are also present in VigiBase).[2,3] This notice aims to further highlight the issue of a continuing problem with children getting access to potentially harmful drugs. This is especially important to bear in mind when prescribing drugs to parents for indications likely to reflect decreased risk awareness. It should be stressed that, when available, blister packages are the preferred choice for parents with young children.

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Prucalopride and Suicidal ideation

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Summary

Suicidal ideation has been identified in association with the gastrointestinal prokinetic agent, prucalopride, as a potential signal from the WHO Global Individual Case Safety Report database, VigiBase®. Prucalopride is the third 5-HT_4 receptor agonist licensed as a prokinetic agent but its highly selective nature represents an advantage over the previously licensed products cisapride and tegaserod which have both been withdrawn due to adverse cardiac effects. While the total number of case reports for suicidal ideation and prucalopride is small, there is evidence of psychiatric events, specifically anxiety, confusional state, and depression, from clinical trial data as well as a notable number of reports of suicidal ideation for tegaserod. Of potential concern is the inconsistency in the labelling for CNS events between the EU and Canada, the two regions in which prucalopride has been approved. The potential for psychiatric adverse events should be acknowledged in the EU as has been done in Canada. Furthermore, with the identification of these case reports of suicidal ideation, a possible recommendation would be for increased surveillance for such events related to suicide. Additionally, the potential for a relationship between adverse events with prucalopride and certain 5-HT_4 polymorphisms should be explored.

Introduction

Prucalopride was licensed for use by the European Medicines Agency in July 2009 and in Canada in December 2011 with an indication for use in the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.[1,2]

Serotonin or 5-hydroxytryptamine (5-HT) acts as a neurotransmitter and paracrine agent that mediates a wide variety of functions, including cognitive and emotional processes, regulation of sleep and food intake, as well as cardiovascular and gastrointestinal mechanisms. To date 14 different 5-HT receptors, classified into seven subclasses, have been identified.[3]

Prucalopride is a dihydro-benzofurancarboxamide derivative which is highly selective and has high affinity for serotoninergic 5-HT_4 receptors. 5-HT_4 receptors are located both in the central nervous system (CNS) and in the peripheral tissues, specifically the gastrointestinal tract. Activation of 5-HT_4 in the gastrointestinal tract promotes gastrointestinal motility and mucosal secretion. Experimental models both in vitro and in vivo have demonstrated that prucalopride facilitates gastrointestinal motility by promoting longitudinal smooth muscle contractility while suppressing the resistance to propulsion due to circular smooth muscle contraction.[4]

The highly selective nature of prucalopride for the 5-HT_4 receptor represents an advantage over previous prokinetic non-selective 5-HT_4 agonists, such as cisapride and tegaserod. Both of these agents have appreciable affinity for other receptors, channels or transporters [e.g. cisapride: human ether-a-go-go-related gene (hERG)/K^+ channel and tegaserod: 5-HT_{1D} and 5-HT_{2B} receptors] which resulted in adverse event profiles (QT prolongation and cardiovascular ischemic events, respectively) which limited their clinical success.[5-7]

The European Summary of Product Characteristics (SmPC) for prucalopride notes the most commonly occurring events to be headache, nausea, diarrhoea, abdominal pain. Other commonly occurring events were dizziness, fatigue, pollakiuria, vomiting, dyspepsia, rectal haemorrhage, flatulence, and abnormal bowel sounds. Uncommon events included palpitations, anorexia, and tremors.[8] The labelling for Health Canada in contrast notes the following events from the Psychiatric disorders SOC: anxiety, confusional state, and depression.[9]

Suicidal ideation is defined as thoughts about self-harm, with deliberate consideration or planning of possible techniques of causing one's own death.[10] Suicidal ideation is more common than suicide attempts or completed suicide.[11] A 1995 study found that 3.3 percent of patients in an urban primary care outpatient clinic reported suicidal ideation.[12] Risk factors for suicidal behaviours include female gender, younger age, fewer years of education, unmarried status and the presence of a mental disorder, with psychiatric comorbidity significantly increasing risk.[13] In addition, some prescription drugs, such as selective serotonin re-uptake inhibitors, can have suicidal ideation as a side effect.

Reports in VigiBase

There were a total of four case reports in the WHO Global Individual Case Safety Report (ICSR) database, VigiBase® as of December 2014 which reported suicidal ideation in association with prucalopride.

The four case reports were submitted from three countries: Germany, the United Kingdom, and Italy. All case reports were received from health care professionals. One of the reports was determined to be a duplicate. Two of the reports described events occurring in females, ages 44 and 61; one report described events occurring in a male whose age was not reported. Time to onset was reported in all cases and ranged from "hours after the first dose" to 16 days after initiation of prucalopride. Prucalopride was withdrawn and the outcome was reported as recovered in all of the cases.

One of the reported cases was the subject of a published case report.[14] It describes a 61 year old female who was in reportedly good health and not taking any other medications. She was initiated on prucalopride 2 mg per day for the treatment of chronic constipation. Within a few hours after oral administration, she experienced suicidal ideation, visual hallucinations, disorientation, and a loss of balance and memory. The drug was withdrawn and symptoms resolved within 24 hours. She had never previously experienced similar symptoms.

There were an additional 27 case reports of suicide ideation with another 5-HT_4 agonist, tegaserod. There were a total of 24 cases from the USA, two from Canada, and one from Mexico. Several of the 27 cases report depression and are complicated by the use of multiple concomitant medications. However, five of these reports document a positive dechallenge.

Literature and Labelling

Three 5-HT_4 receptor agonists have been variously approved for use as prokinetic agents. The first approved agent was cisapride which has subsequently been removed from both the US and EU markets secondary to cardiovascular events, specifically QT-prolongation.

A second agent, tegaserod, was initially licensed in the US for the treatment of irritable bowel syndrome, but an observed increased risk in myocardial infarctions and strokes led to its withdrawal five years after approval. Tegaserod was never approved for use in the EU. In the refusal assessment report from the EMA's Committee for Human Medicinal Products (CHMP), it is noted that findings in mice safety pharmacology studies suggest certain CNS related effects, such as increased activity, abnormal gait, and hypothermia at doses 10 to 100-fold higher than therapeutically relevant. Furthermore, it is reported that 2.1% of all tegaserod subjects reported adverse events in the Psychiatric disorders SOC (compared to 1.6% in placebo subjects). There were a total of six deaths in subjects taking tegaserod during clinical development, two of which were reported as suicide (12,032 total subjects

Table 1. Characteristics of reports for prucalopride and suicidal ideation in VigiBase®

Case	Age/ Sex	Medical history	Suspected (S) or concomitant drugs (C)	Time to onset	Indication	Dechallenge/ Rechallenge	ADR terms (WHO-ART)	Outcome
1	-/M	Not provided	Prucalopride (S) Beta blocking agents (C)	3-4 days	Chronic constipation	Withdrawn	Suicidal ideation, off-label use	Recovered
2	44/F	Not provided	Prucalopride (S) Paracetamol, mebeverine, tramadol, fluocinonide, levothyroxine, omeprazole, propantheline, pregabalin, morphine, hyoscine (all C)	16 days	Constipation	Positive dechallenge	Suicidal ideation, thoughts of self harm, depression	Recovered
3	61/F	None	Prucalopride (S) Brotizolam (C)	Hours after first dose	Chronic constipation	Positive dechallenge	Suicidal ideation, balance difficulty, prostration, hallucination visual, amnesia, disorientation	Recovered with sequelae

in the safety database received tegaserod); no deaths were felt by the investigator to be related to study drug. CNS/psychiatric events were considered to be an outstanding safety issue.[15]

Prucalopride is the third 5-HT_4 receptor agonist. It has not been approved for licensure in the US; however, it was approved for use in chronic constipation in the EU in 2009 and in Canada in 2011. In the Committee for Medicinal Products for Human Use approval assessment report, it is noted that in single dose toxicity studies performed on mice that there were CNS effects seen "at very high doses" However, there was no discussion in the report regarding events from the Psychiatric disorders SOC. There were two deaths in the double-blind placebo controlled trials and four deaths in open-label studies. The report notes only that none of the deaths were considered related to treatment by the investigator. Neither suicidal ideation nor other CNS events are included in the risk management plan for prucalopride.[1] In contrast, the Summary Basis of Decision for Health Canada notes that prucalopride: "…may act on receptors in the brain having the following 5-hydroxytryptamine (5-HT) receptors: 5-HT_1; 5-HT_2; and 5-HT_3; that could be involved in anxiety and depression. It is unclear whether 5-HT_4 may be related to depression and anxiety. However, anxiety has been reported in many clinical studies and some cases were reported as serious events. The open-label studies recorded anxiety in 1.9% of the patients treated with the 2 mg dose, and similar results were found with 4 mg dose. In these studies, depression was elicited at a higher incidence than anxiety (3.5% versus 1.9%) with the 2 mg dose."[2]

The 5-HT_4 receptor (5-HT_4-R) is located both in the CNS and in the peripheral tissues. In the human brain, 5-HT_4-Rs have been localized in the basal ganglia, the hippocampal formation and the cortical mantle.[3] It could be hypothesized that prucalopride, acting upon the 5-HT_4 receptors in the basal ganglia could lead to a syndrome of dysphoria and suicidal ideation, as substantia nigra hyperactivity has been implicated in schizophrenia.[11] Also, available evidence for another serotonin receptor agonist, metoclopromide, suggest that different polymorphisms in 5-HT_4 receptor HTR4 genes are associated with adverse events and clinical effectiveness. There is the potential that only patients with certain genetic variations in the 5-HT_4 receptor are susceptible to neuropsychiatric side effects.[16]

Discussion and Conclusion

The signal for a possible association between prucalopride and suicidal ideation is based upon only three cases. It is notable that in none of the cases are there any past histories of depression or concomitant medication use implying a history of psychiatric disorders. Furthermore, the time to onset is relatively short for two of the cases, within hours to days. All cases had documentation of resolution of symptoms after drug withdrawal.

The highly selective nature of prucalopride has been the focal point of the development of this agent given the limitations of its predecessors. To this end, multiple preclinical investigations into the cardiac effects have been completed and showed a lack of interaction with the hERG potassium channel and 5-HT_{1D} and 5-HT_{2B} receptors. Both approval reports from the EU and Canada thoroughly described this data. However, there is an inconsistency in the presentation of data regarding potential psychiatric effects between the EU and the Canadian reports. As a result, there is no labelling for such events in the EU SmPC (or inclusion of these events into the Risk Management Plan) but the inclusion of the events of anxiety, confusional state, and depression in the Canadian label.

It is clear that prucalopride represents therapeutic alternative with an improved safety profile and that the signal for an association with suicidal ideation is weak at the current time. However, the potential for psychiatric adverse events should be acknowledged in the EU as has been done in Canada. Furthermore, with the identification of these case reports of suicidal ideation, a possible recommendation would be for increased surveillance for such events related to suicide. Additionally, the potential for a relationship between adverse events with prucalopride and certain 5-HT_4 polymorphisms should be explored.

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Response from Shire

Suicide-related events include passive and active thinking, planning, and finally taking action to commit suicide. Passive death thoughts are common in the general population. In a cross-national (17 countries) sample, Nock et al estimated the lifetime prevalence of suicidal ideation at 9.2% (1).

For prucalopride there was no signal for suicide-related events in the developmental clinical trials of this product for chronic constipation.

The Shire global safety database contains the same postmarketing reports tabulated by the authors and, except for one duplicate, no other report of suicide-related events.

In review of the three postmarketing cases in the database, the first case involved a male of unknown age and was derived from sparse documentation which included no information on medical history or concurrent disorders. The second case involved a 44-year old female who was concomitantly treated with tramadol, a medication with a known association with suicidal events and depression (2,3).

The third and most recent case was presented as a published case report where suicidal thoughts were reported amongst a plethora of other events including balance difficulty, prostration, visual hallucinations, amnesia and disorientation. Interestingly, the publication failed to mention this patient's concomitant treatment with brotizolam, a benzodiazepine. The constellation of events described is considered to be clinically compatible with a paradoxical benzodiazepine reaction given that such reactions may typically include hallucinations, inconsolable crying, agitation, restlessness, disorientation, aggressive behavior and/other psychological phenomena (4). Additionally, benzodiazepine use has been identified in at least one published study as among a number of variables associated with suicide in older adults (5).

In summary, suicide-related events did not constitute a signal during clinical development of prucalopride. In the postmarketing review, 2 of the 3 case reports of suicidal ideation were confounded by potentially relevant concomitant medication exposures, and the third case report was poorly documented. Based on the information available at this time, Shire does not believe there is sufficient evidence to support a causal association of suicidal ideation with the use of prucalopride.

For Shire,

Anders Lindholm MD, PhD

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Temozolomide and Oesophagitis

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Summary

Temozolomide is an oral alkylating agent used in a radiation-containing regimen as the first-line treatment for glioblastoma. Oesophagitis is not listed in the EMA SmPC or FDA label, while, related reactions such as stomatitis, dysphagia and gastroenteritis are. In a series of nine cases from the WHO Global Individual Case Safety Report database, VigiBase®, a relationship between temozolomide and oesophagitis has been highlighted through the vigiRank screening method. Though the information coming from this series is not fully conclusive by itself and there is no clear evidence in the literature of this combination, both biological plausibility and analogy to a structurally similar drug indicate that this reaction could be correlated to temozolomide; further studies should be pursued to characterize it.

Introduction

In September 2014, the UMC signal detection for the first time screened reports issued for paediatrics. This screening, using the vigiRank screening method, highlighted an association between temozolomide and oesophagitis. Since the drug is not restricted to paediatric use and multiple age groups were associated with the adverse event, this evaluation was conducted on patients of all ages.

Temozolomide is an oral triazene alkylating agent that has been available since the early 2000s; coupled with radiotherapy it is the first-line treatment for glioblastoma, the most common primary brain cancer in adults, against which its efficacy has been proven.[1,2] At physiological pH, temozolomide is converted to the monomethyl-triazene metabolite, MTIC, which exerts the main cytotoxic action by methylating DNA at a number of sites. Temozolomide shares this metabolite and structural similarities with another triazene alkylating agent, dacarbazine.[3] In early clinical development it was observed that the administration of a single dose of temozolomide induced myelosuppression.

Oesophagitis is a potentially serious inflammation of the oesophagus that can occur due to different causes, from infections to physical injury resulting from radiation therapy.

Reports in VigiBase

Twelve cases of oesophagitis (WHO-ART preferred term) in association with temozolomide were identified in the WHO Global Individual Case Safety Report database, VigiBase®, in October 2014. Based on age, sex, country, type of report and other features, one duplicate (case 1) and one triplicate (case 8) have been identified. Thus, there are nine primary cases containing the reaction of interest (Table 1); in one, the reaction was reported as "oesophageal pain".

Age and sex were known in five cases while two cases only reported patient gender (Table 1). Two cases concerned children, an 8-year-old female and a 10-year-old male, while three involved male adults aged 62, 67 and 69; two cases of unknown age were female, while two cases had no information on the patient. No age or sex patterns emerge.

In all cases the reaction appeared after the intake of the drug. Two reported time to onset (19 days and 31 days); in none was the reaction reported alone. Temozolomide was the only suspected drug in three of the reports. The drug was withdrawn in four cases: the outcome was unknown for two cases (1, 8), recovery as concerns one (case 2, which was reported as positive dechallenge) and no recovery in another (case 3). There is no information on dechallenge in case 7, however the outcome was recovery. No cases mention positive rechallenge. All cases except one, case 3, were considered as serious. In two cases the patient died due to severe myelosuppressive reactions.

In November 2014 VigiBase was also queried for oesophagitis (WHO-ART) in association with dacarbazine, obtaining seven cases. Additionally, this combination was highlighted through a disproportionality analysis with an IC of 1.29 and IC_{025} of 0.03.

Literature and labelling

Temozolomide is indicated for use in children from three years of age and in adults. Oesophagitis is not labelled for the drug in adults or in children, neither in the UK SPC nor the FDA label, however, stomatitis, dysphagia and gastroenteritis are listed as adverse drug reactions.[4,5] Using the keywords "temozolomide" and "oesophagitis" (or "oesophag*") no articles were retrieved in PubMed (November, 2014). In two separate clinical studies, two cases of oesophagitis associated with temozolomide were reported;[6,7] it is difficult to

Table 1. Characteristics of reports for temozolomide and oesophagitis in VigiBase®

Case	Age/ Sex	Other Suspected (S) or concomitant (C) drugs	Other reported reactions (WHO-ART preferred terms)	Time to onset	Action taken/ Outcome	Comments
1	62/M	Cisplatin, gemcitabine, methylprednisolone, paclitaxel (all S) Acetylsalicylic acid, therapeutic radiopharmaceuticals (both C)	Venous thrombosis, thrombocytopenia, pancytopenia, myopathy, hiatus hernia, chest pain, ulcer*	-	Drug withdrawn/ Unknown	Oesophageal candidiasis
2	67/M	Zolpidem, amlodipine, naproxen, tolteridine, vitamins nos, travoprost, paracetamol (all C)	Vomiting, nausea, haematemesis, gastro-intestinal disorder nos, erythema, constipation, chest x-ray abnormal, aortic disorder*	-	Dechallenge positive	-
3	69/M	Metamizole, corticosteroids, omeprazole, tramadol, therapeutic radiopharmaceuticals (all C)	Thrombocytopenia	31 days	Drug withdrawn/ Not recovered	Not serious
4	-/F	Bevacizumab, irinotecan, therapeutic radiopharmaceuticals, fluticasone, levothyroxine, simvastatin, dexamethasone, pindolol, fexofenadine, citalopram, phenytoin, bupropion, tolterodine, paracetamol/hydrocodone bitartrate, trazodone, omeprazole (all S)	Wbc abnormal nos, urinary tract infection, neutrophil count*, haemoglobin*	19 days	-	Developed oesophagitis after stopping temozolomide (duration 4 days). Sepsis.
5	-/F	Topotecan, bevacizumab (both S) Sertraline, metoprolol (both C)	Thrombocytopenia, sepsis, renal failure, oesophagitis, neutropenia, neoplasm progression*, mucosal inflammation, mental status changes*, febrile neutropenia, thrombosis venous deep	-	-	Febrile neutropenia, death due to infection
6	10/M	Irinotecan, carboplatin, etoposide, cyclophosphamide (all S) Hydromorphone (C)	Mucosal inflammation, febrile neutropenia, platelet count decreased, appetite decreased, oesophageal pain, abdominal pain upper, anaemia	-	-	Oesophageal pain
7	-/-	-	Incorrect technique in drug usage process, angioedema, oesophagitis	-	-/Recovered	-
8	8/F	Nimotuzumab (S)	Dermatitis, leucopenia, thrombocytopenia	-	Drug withdrawn/- Rechallenge/-	Death due to disease progression
9	-/-	Bevacizumab (S)	Vomiting, transaminase nos increased, dehydration, wound infection, healing impaired, intestinal perforation, haemorrhage nos, fatigue, venous thrombosis, neutropenia, thrombocytopenia	-	-	-

**MedDRA terms*

ascertain if these cases are the ones that have been reported and stored in VigiBase. At least one, case 8, that was presented in Reactions Weekly, has already been sent to VigiBase.

Discussion and Conclusion

Oesophagitis can be a serious reaction that may have many causes; among them, radiation therapy that is usually employed along with temozolomide for the treatment of brain tumours. Another cause is myelodepression and subsequent neutropenia, which in turn can give rise to infections. Medications, through different mechanisms, have also been associated with oesophagitis; particularly antitumorals. Myelodepression, for instance, can be induced by different drugs; in fact, some of the cases in the present series (1, 5, 6, 9) developed neutropenia or candidiasis. Direct damage could be another possibility, as temozolomide is administered by the oral route. Thus, based on the pathophysiology of the reaction and the mechanism of this alkylating agent, there exists the possibility that this reaction was cause-related.

The present series is composed of nine cases; some of the cases (2, 3, 6, 9) come from clinical studies and are well described, as is the one from the literature (case 8). However, there is only one case (case 7) in which temozolomide is the only reported drug; since this case is not sufficiently complete, the possibility of unreported concomitants cannot be excluded. Although there is one positive dechallenge, there is no case with a positive re-challenge: based on this particular series, drawing a conclusion proves to be difficult.

In the literature there are some cases of oesophagitis,[6,7]

but once again, it is difficult to pinpoint the reaction to temozolomide since most of the patients were being treated with multiple drugs.

All in all, the best evidence could be pharmacological plausibility. Many anticancer drugs are able to interfere with the cellular cycle, and in this manner interrupt the cellular growth; this is particularly evident in rapidly growing tissues. For these drugs, stomatitis, oesophagitis, gastritis and enteritis would be a continuum depending on the route, dose and time of exposure. With this in mind, it would be expected for similar adverse reactions to occur. In fact, stomatitis, dysphagia and gastroenteritis are already labelled for temozolomide.

Oesophagitis is therefore a possible reaction in connection with temozolomide. Moreover, an error in the administration could possibly account for this reaction. In fact, one of the cases mentions an "incorrect technique in drug usage process"; the Summary of Product Characteristics does warn about this possibility: the capsules have to be swallowed as they are, with water; they must not be opened or chewed.

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Vemurafenib and Thrombocytopenia

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Summary

Vemurafenib is a protein kinase inhibitor with activity against mutated B-RAF protein; it is used in the treatment of metastatic or unresectable malignant melanoma that carries the BRAF V600E mutation. B-RAF protein acts in the RAS-RAF-MEK-ERK intracellular signalling pathway that leads to cell growth and proliferation: by targeting mutated B-RAF, vemurafenib inhibits the growth of melanoma cells containing the mutated B-RAF gene. At the time of assessment (March 2015), The WHO Global Individual Case Safety Report (ICSR) database, VigiBase® contains 28 ICSRs in which vemurafenib is associated with thrombocytopenia (after exclusion of two duplicates). One case provides information that suggests a 'certain' causal relationship between vemurafenib and thrombocytopenia, four cases suggest a 'probable' causal relationship and a further 14 cases can be assessed to have a 'possible' causal relationship to vemurafenib. Six cases include co-reported ADR terms that indicate a more widespread myelosuppression, rather than an isolated thrombocytopenia. The RAS-RAF-MEK-ERK intracellular signalling pathway is involved in the production and differentiation of haematopoietic progenitor cells. It is possible that thrombocytopenia associated with vemurafenib may be part of a spectrum of drug induced myelosuppression, possibly brought about through an effect on the RAS-RAF-MEK-ERK intracellular signalling pathway in haematopoietic progenitor cells.

Introduction

Vemurafenib is a serine-threonine protein kinase inhibitor that inhibits the kinase activity of mutated B-RAF protein. The RAS-RAF-MEK-ERK mitogen activated protein kinase (MAPK) cascade is an important cytoplasmic signalling pathway involved in the regulation of normal somatic cell proliferation. Mutations in the genes encoding components of this pathway have been associated with a number of human cancers.[1] An activating mutation in the BRAF gene, which encodes the serine-threonine protein kinase B-RAF, has been found to be present in 40-60 percent of melanomas, most commonly the BRAF V600E mutation.[2] Vemurafenib is indicated for the treatment of metastatic or unresectable melanomas that carry the BRAF V600E mutation. The recommended dose is 960 mg twice daily and it is currently available in 240 mg tablets.[3] Vemurafenib has also been used off-label for other types of malignancy carrying the BRAF V600E mutation.

Thrombocytopenia is defined as a platelet count of less than 150 x 10^9/L (150 000 per μL). A grading system for thrombocytopenia has been developed by the United States National Cancer Institute in which platelet counts between 75 x 10^9/L and 150 x 10^9/L are classified as Grade 1, while platelet counts below 25 x 10^9/L are classified as Grade 4.[4] Patients with platelet counts above 20 x 10^9/L are usually asymptomatic, but the risk of spontaneous mucocutaneous bleeding (gingival bleed, epistaxis, menorrhagia, petechiae and ecchymoses) and life-threatening, spontaneous intracranial hemorrhage or gastrointestinal bleeding increases rapidly with platelet counts below 10 x 10^9/L.

Thrombocytopenia in the context of metastatic malignancy may result from a number of causes including metastatic infiltration of the bone marrow, sepsis, disseminated intravascular coagulation (DIC), radiation and drugs. Drug-induced thrombocytopenia (DIT) is associated with many drugs and results from either decreased platelet production or increased platelet consumption. Decreased platelet production as a consequence of generalized myelosuppression is a relatively common adverse effect of many chemotherapeutic drugs, while selective suppression of megakaryocyte production leading to isolated thrombocytopenia has been associated with thiazide diuretics, alcohol and tolbutamide. Increased platelet destruction is further categorized as either immune or non-immune: drug-induced immunologic thrombocytopenia (DITP) is associated with a large number of drugs (most notably heparin) and several immunologic mechanisms have been identified. Non-immune platelet destruction such as TTP-HUS (thrombotic thrombocytopenic purpura – haemolytic uraemic syndrome) occurs less commonly, in association with a small number of anti-neoplastic agents.[5]

Reports in VigiBase

At the time of assessment (March 2015), there were 30 individual case safety reports (ICSRs) of thrombocytopenia in association with vemurafenib in the WHO Global ICSR database, VigiBase®. Two duplicates were identified bringing the number of assessed case reports to 28. The reports came from

10 countries: United States (9), France (8), Germany (4) and Austria, Colombia, Italy, Netherlands, Norway, Turkey and United Kingdom (1 each). Twenty-three of the ICSRs were serious and three reports were fatal.

The cases concerned 9 males and 19 females. Age was reported for 24 cases and ranged from 37 to 70 years (median age 56.5 years).

The indication for treatment was reported as malignant melanoma in 21 cases, colorectal cancer in one case and hairy cell leukaemia in one case; in the remaining five cases, the indication for treatment was reported either as unknown (three cases) or was not stated (two cases). Vemurafenib was the only suspected drug in 21 of the 28 cases: in 14 of these cases, vemurafenib was the only reported drug while the other seven cases reported concomitant medicines. In the remaining seven cases, other medicines for which thrombocytopenia is a known potential adverse effect were also suspected, including oxaliplatin, fluorouracil, cladribine, fotemustine, rituximab, aflibercept, levetiracetam, valproic acid, carvedilol, spironolactone, piperacillin/tazobactam and a combination medicine containing chlorpheniramine. Two of these ICSRs also reported co-suspected medicines that are not known to be associated with thrombocytopenia, including clobazam, folinic acid and caffeine/paracetemol/papaver somniferum latex. The total daily dose of vemurafenib was reported in half of the cases and ranged from 240 mg to 1920 mg (median dose 1920 mg).

The time-to-onset was reported for 12 cases and ranged from 3 to 225 days, with a median time-to-onset of 20 days. Vemurafenib was withdrawn following the onset of thrombocytopenia in 12 cases: dechallenge was positive in eight of these cases, negative in one case and the outcome of dechallenge was not stated in the remaining three cases. In one case the dechallenge action was reported as dose reduced but the dechallenge outcome was not reported. In six cases the dechallenge action was reported as 'dose not changed': thrombocytopenia resolved in two of these cases, no effect was observed in two cases and the effect was unknown in two cases. The dechallenge action was reported as unknown in four cases, was not reported in three cases and was not applicable in two cases (due to the death of the patient). In three of the cases with a positive dechallenge, vemurafenib was subsequently reintroduced at a lower dose: one case reported recurrence of thrombocytopenia (positive rechallenge) while the remaining two cases reported no recurrence. The outcome for thrombocytopenia was reported in 19 of the cases as follows: recovered (7), recovering (4), not recovered (6) and died (2). For the remaining nine cases, the outcome was reported as unknown.

Literature and Labelling

Thrombocytopenia is not listed as a possible ADR for vemurafenib in any of the sources that were checked, including the EMA[6], UK Summary of Product Characteristics[7] and the US FDA Product Label.[3] Neutropenia is the only haematological ADR listed in the product information.

Discussion

In this series of 28 ICSRs in which vemurafenib is associated with thrombocytopenia, one case met the criteria for a 'certain' causal relationship between the suspected drug and the reported ADR according to the WHO-UMC System for Case Causality Assessment.[8] Four cases had sufficient evidence to suggest a 'probable' association and a further 14 cases could be considered 'possible'. These 19 cases are summarised in Table 1. Bony infiltration associated with metastatic malignant melanoma (the indication for 21 of the 23 cases in which this information was provided) should be considered a risk factor for thrombocytopenia in each of these cases.

Case 22 provides the strongest evidence in this series for a causal relationship between vemurafenib and thrombocytopenia in that it has a plausible time relationship to drug exposure, no alternative explanation for the ADR, a positive dechallenge and a positive rechallenge. The case concerns a 65 year old female with a history of end-stage renal disease, arterial hypertension and a previous DVT. Thrombocytopenia and anaemia developed 19 days after initiation of treatment with vemurafenib for melanoma, and pancytopenia with febrile neutropenia developed on day 22 of therapy. Platelets were transfused. Vemurafenib was stopped for six days, during which time the platelet count improved; vemurafenib was then reintroduced at half the original dose but three days later the platelet count had again dropped, consistent with a positive rechallenge. Vemurafenib was stopped definitively and the platelet count returned to normal. Clinical investigations ruled out alternative explanations for the thrombocytopenia.

Cases 2, 3, 5 and 13 could be considered to have a 'probable' causal relationship. The time-to-onset (TTO) for three of these cases ranged from 15-29 days; TTO was not stated for the fourth case but other

Table 1. Cases of interest in VigiBase® of vemurafenib and thrombocytopenia

Case	Age / Sex	Other suspected (S) or concominant (C) drugs	Other reported ADRs (WHO-ART Preferred Term)* *(Reported terms in italic- included where more informative)*	Time to onset (days)	Dechallenge / Rechallenge	Outcome at time of reporting
2	58/F	Zolendronic acid (C)	Bilirubinaemia, rash	20	Withdrawn, reaction abated Subsequently reintroduced at a lower dose with no recurrence	Recovered
3	66/M	-	Oedema, generalised oedema, neoplasm, musculoskeletal pain, pulmonary oedema, duodenal ulcer, GI haemorrhage	-	Withdrawn, reaction abated	Recovered
5	51/M	-	**Leukopenia, pancytopenia**, paralysis facial	29	Withdrawn, reaction abated	Recovered
6	53/F	-	-	< 7	Withdrawn	Unknown
7	58/M	-	- (Pneumonia)**	46	Withdrawn, reaction abated	Recovering
11	53/M	Levetiracetam, omeprazole (both C)	**Anaemia, leukopenia**	43	-	Died
12	-/F	-	Bronchitis, *black eye*	4	Withdrawn, reaction abated	Recovering
13	68/F	-	Haemorrhage, **leukopenia**	15	Withdrawn, reaction abated	Recovering
14	68/F	-	-	7	Unknown	Not recovered
15	61/M	Gabapentin (C)	Disseminated intravascular coagulation, haematoma, *venipuncture site haemorrhage*, urinary tract infection, *soft tissue haemorrhage,* haematuria, fibrinolysis increased, C-reactive protein increased, leukocytosis, *skin haemorrhage*, haematoma, anaemia, *metabolic disorder*	3	Withdrawn	Not recovered
17	70/F	Piperacillin/tazobactam (S) Allopurinol, amlodipine, clonidine, colchicine, daptomycin, darbepoetin alfa, diphenhydramine, enoxaparin, famotidine, insulin glargine, ipratropium, lisinopril, megestrol, methylprednisolone, omeprazole, prednisolone, salbutamol, simvastatin, sodium bicarbonate, sulfamethoxazole/ trimethoprim, tigecycline, timolol, tobramycin (all C)	Palmar-plantar erythrodysaesthesia, bronchitis, infection bacterial, AST increased, acidosis, pulmonary congestion, hyperglycaemia, pancreatitis, pleural effusion, gastric dilatation, infection staphylococcal, fibrillation atrial, cerebral disorder, renal failure chronic, hyperuricaemia, bilirubinaemia, tachycardia ventricular, ECG abnormal specific, candidiasis, alkaline phosphatase increased, medical device complication, respiratory insufficiency, urinary tract infection, failure to thrive, atelectasis, bilirubinaemia, cardiac arrest, neuropathy peripheral, ALT increased, dermatitis exfoliative	-	Not applicable	Unknown
18	52/F	-	Dehydration, *disease progression*, **white blood count decreased**, infection	-	Not applicable	Died
20	44/M	Carvedilol, spironolactone , saffeine/paracetemol/papaver somniferum latex (all S)	-	163	Dose not changed, no effect	Not recovered
22	65/F	Atenolol, sodium polystyrene sulfonate, furosemide, losartan, sevelamer, calcifediol, prasozin, paracetamol, esloratadine (all C)	**Anaemia, pancytopenia, febrile neutropenia**	19	Withdrawn, reaction abated Restarted 6 days later with recurrence of thrombocytopenia	Recovered
23	56/F	Folic acid, cyanocobalamin (both C)	Fever, urinary tract infection, arthropathy, arthrosis, rash, *mass*, rash erythematous, hypokalaemia, haemorrhage nos, alopecia, pruritis, hepatic enzymes increased, arthralgia, arthritis, *joint swelling*	-	Drug withdrawn, reaction abated Drug restarted with no recurrence of thrombocytopenia	Unknown
24	64/F	-	-	169	-	Not recovered
26	38/F	Fotemustine, polyvalent immunoglobulins (both C)	**Neutropenia**	79	Dose not changed, no effect	Not recovered
27	37/F	-	-	55	Dose not changed, outcome unknown	Unknown
28	38/F	-	Purpura, *bruising of leg*	> 122	Dose not changed, outcome unknown	Unknown

**Co-reported ADR terms highlighted in bold suggest a more widespread myelosuppression rather than isolated thrombocytopenia*

***Case 7: Narrative states that patient was hospitalised for pneumonia when thrombocytopenia was diagnosed*

information provided in the report indicates that the reaction occurred between 6 and 10 weeks after starting vemurafenib. In each of these four cases vemurafenib was withdrawn and the thrombocytopenia resolved; in Case 2, the drug was subsequently restarted at a lower dose with no recurrence of the ADR. No other drugs were suspected in any of the four cases (in three cases vemurafenib was the only reported drug).

The remaining 14 cases shown in Table 1 could be considered to have a 'possible' causal relationship to vemurafenib. The time-to-onset for these 14 cases, where reported, ranged from 3 to 169 days. Two of the cases reported co-suspected medicines known to be associated with thrombocytopenia: piperacillin/tazobactam (Case 17) and carvedilol, spironolactone (Case 20). The latter case also reported the combination analgesic caffeine/paracetemol/papaver somniferum latex as suspected, but it is not known to be associated with thrombocytopenia. Levetiracteam, which is known to be associated with thrombocytopenia, was listed as a concomitant medicine in Case 11. Among these 14 cases, three cases reported evidence of a positive dechallenge (Cases 7, 12 and 23), one of which subsequently restarted vemurafenib with no recurrence of thrombocytopenia (Case 23). Concurrent infections including pneumonia and urinary sepsis may have accounted for the thrombocytopenia in each of these cases, and Case 23 was also confounded by other medicines.

The remaining six cases (not shown in Table 1) lacked sufficient evidence to suggest a causal relationship between vemurafenib and thrombocytopenia. In Case 8, the patient received radiation therapy to the lumbar vertebrae one day prior to starting treatment with vemurafenib and the thrombocytopenia improved while treatment with vemurafenib continued; in Cases 9 and 16, the thrombocytopenia appears to have preceded treatment with vemurafenib, and in Cases 25, 29 and 30, the temporal relationship to other medicines provides a more plausible alternative explanation for the thrombocytopenia. Causality could not be assessed for the remaining three cases (Cases1, 4 and 10) due to a lack of information in the reports.

Vemurafenib acts on mutated B-RAF protein to inhibit the RAS-RAF-MEK-ERK intracellular signalling pathway in melanoma cells to prevent cell growth and proliferation. This same pathway is also present in haematopoietic progenitor cells and plays a role in haematopoietic cell differentiation[9,10], suggesting a possible mechanism by which vemurafenib might cause thrombocytopenia. Platelets (thrombocytes) are formed from megakaryocytes, which derive from the multipotential hematopoietic stem cell (HSC). The HSC gives rise to progressively committed progenitor cells, including the common myeloid progenitor (CMP) and the megakaryocyte-erythroid progenitor (MEP). MEPs in turn give rise to both megakaryocytic and erythroid cell lineages. Multiple transcription factors are involved in the differentiation of these MEPs to megakaryocytes, the most important of which is thrombopoietin (TPO). Binding of TPO to the TPO receptor on the MEP cell surface membrane activates the intracellular signaling protein Jak2, which in turn activates several intracellular signaling cascades, including the RAS-RAF-MEK-ERK cascade.[11]

Six of the cases shown in Table 1 include co-reported ADR terms that indicate a more widespread myelosuppression, rather than an isolated thrombocytopenia (Cases, 5, 11, 13, 18, 22 and 26). These co-reported terms are highlighted in bold in Table 1. Granulocytopenia has previously been signalled for vemurafenib (SIGNAL, issue 3, 2013) and neutropenia has since been added to the US, UK and EMA product information sheets, adding support to the notion that vemurafenib may affect the RAS-RAF-MEK-ERK cascade in haematopoietic cells. It is possible that all of these cases in which vemurafenib is associated with depression of various blood cell lineages may represent a spectrum of drug induced myelosuppression, possibly brought about through an effect on the RAS-RAF-MEK-ERK intracellular signalling pathway in haematopoietic progenitor cells.

Conclusion

The data provided in the case series strongly supports a signal for the association between vemurafenib and thrombocytopenia. The suggestion of a possible mechanism, although speculative, adds further support for the signal.

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Response from Roche

In March 2015 the WHO Monitoring center in Uppsala invited Roche to comment on a signal of thrombocytopenia in patients treated with vemurafenib. WHO cited 28 cases of thrombocytopenia associated with vemurafenib treatment in the VigiBase®. The report concluded that the data provided in their case series strongly supports a signal for the association between vemurafenib and thrombocytopenia.

Drug induced thrombocytopenia has a reported frequency of approximately 19% to 25% in acutely ill patients. Clinical manifestation usually consists of moderate to severe thrombocytopenia (platelet count of less than 50×10^9/L) and spontaneous bleeding which could be potentially life threatening. (Visentin & Liu, 2007) Typically, the thrombocytopenia occurs 1 to 2 weeks after the introduction of a new drug or 2-3 days after a single dose when a drug has previously been taken intermittently. Demonstration of drug-dependent anti-platelet antibodies is important to confirm the etiology of drug-induced thrombocytopenia. Recovery from drug-induced thrombocytopenia usually begins within 1 to 2 days of stopping the drug and is typically completed within a week. Drug-dependent antibodies can persist for many years.

Several mechanisms have been described in the pathogenesis of drug-induced thrombocytopenia, with accelerated platelet destruction in the presence of the offending drug as the most common immune mechanism. Non immune platelet destruction associated with a small number of antineoplastic agents, such as bleomycin, can occur in thrombotic microangiopathy and its variant form, hemolytic uremic syndrome. (Goerge & Aster, 2009)

The literature describes case reports of thrombocytopenia in metastatic melanoma patients as part of massive bone marrow infiltration (Deepali, Daga, & et Al, 2007), secondary to chemotherapy or immunotherapy (e.g., ipilimumab, high dose IL2), and secondary to platelet consumption in disseminated intravascular coagulation (Lepelley-Dupont, Chevrant-Breton J, & et Al, 2009). We performed an analysis on the background incidence rate of secondary thrombocytopenia and all thrombocytopenia in patients with metastatic melanoma using the Truven Healthcare MarketScan® Commercial Claims and Encounters (Commercial) database. The incidence of thrombocytopenia following a diagnosis of metastatic melanoma was estimated as 5.93 (secondary thrombocytopenia) and 42.2 (all thrombocytopenia) per 1,000 patient years.

Vemurafenib inhibits mutant $BRAF^{V600}$ and is approved for the treatment of adult patients with metastatic melanoma harboring this mutation. Currently the vemurafenib label does not include thrombocytopenia as an adverse drug reaction. Preclinical studies do not support a direct association with thrombocytopenia, however one case of bone marrow necrosis was noted in one of two moribund sacrificed dogs in the prematurely terminated 39-week dog study (Roche, 2015). In the Phase III trial, <1 % of 337 patients dosed with vemurafenib reported thrombocytopenia.

As of March 24, 2015, there are 45 cases of thrombocytopenia related adverse events (AEs) reported with vemurafenib use in the Roche safety database, thirty-two of which were assessed as serious. Median age was 59.5 years (31-80). Gender was provided for 43 cases of which 22 were males and 21 were females. Indication was provided for 33 cases of which 32 were malignant melanoma cases and one case was hairy cell leukemia. Latency was provided for 20 of the 45 cases. Median latency was 24 days with a range of 3-225 days. Thirteen of these 20 cases had a latency of ≤ 30 days.

Based on medical review, 6 out of the 45 cases were assessed to have a likely causal association to vemurafenib. The remaining cases were: a. lacking vital information that makes meaningful assessment difficult (n=20), b. have an unlikely causal association based on strong alternative etiology for the event of thrombocytopenia such as concomitant use of fotemustine, bone marrow infiltration by melanoma cells, or secondary to microangiopathy or DIC (n=13); and c. assessed to have possible causal association based on the latency that was longer than expected for drug-induced thrombocytopenia or a negative dechallenge/rechallenge (n=6).

Table 1 below provides the case details on the 6 cases that are assessed to have a likely causal association based on case presentation, temporal association, and dechallenge information. Of the 6 cases, two cases had associated depression of other blood cell lineage.

Table 1. Cases of interest in Roche Vemurafenib Safety Database

Case	Age Gender	Concom Medication	Indication	Initial total daily dose	Adverse Event Term	Other Reported Adverse Events	Highest CTCAE Severity Grade	AE Duration (days)	Latency (days)	Event outcome	Reporter Causality	Vem outcome	Dechall	Rechall
1	Unk Female		Unknown indication	1920mg	Platelet count decreased	Lower respiratory tract infection Periorbital contusion	3	Not reported	4	Resolving	Related	D/C	Positive	N/A
2	66 Male		Malignant melanoma	1920mg	Thrombocytopenia	Gastrointestinal haemorrhage Duodenal ulcer Pulmonary oedema Musculoskeletal pain Neoplasm Generalised oedema	2	7	15	Resolved	Related	D/C	Positive	N/A
3	Unk Male	Saquinavir Bisoprolol Aspirin Simvastatin Allopurinol Prednisolone	Malignant melanoma	1920mg	Platelet count abnormal	Rash Pruritus	4	N/A	11	Resolving	Related	D/C	Positive	N/A
4	51 Male		Malignant melanoma	480mg	Thrombocytopenia	Leukopenia Facial paresis	3	7	29	Resolved	Related	D/C	Positive	N/A
5*	65 Female	Furosemide Losartan Sevelamer Atenolol Prozosine	Malignant Melanoma	Not reported	Thrombocytopenia	Anemia Pancytopenia Febrile neutropenia	4	8; 17 (2nd episode)	22; 3 (2nd episode)	Resolving to grade 1; Resolved (2nd episode)	Related	Interrupted and dose reduced; D/C (2nd episode)	Positive**; Positive	Positive; N/A
6	58 Female	Zoledronic Acid	Unknown indication	1920mg	Thrombocytopenia	Rash Blood bilirubin increased	2	NR	20	Resolved	Not reported	Interrupted and dose reduced	Positive	Negative

*Legend: *Case number 22 in the WHO report; vem = vemurafenib; D/C = discontinued; N/A = not applicable; dechalle=dechallenge; rechalle=rechallenge; ** confounded by platelet treatment*

AER number 1351266 was identified in the WHO Report as case 22 and where causal relationship between vemurafenib and thrombocytopenia was described as "certain" in that report. Similarly, Roche assessed this case to be likely associated with vemurafenib treatment.

The 6 cases of thrombocytopenia yield a crude reporting rate of 0.67 cases per 1000 patient years based on an estimated cumulative patient exposure to vemurafenib of 17,729 patient years. Using a conservative approach, the crude reporting rate of 45 cases is 2.54 per 1,000 patient years. These rates are significantly lower than expected for the metastatic melanoma population based on the Marketscan analysis.

Roche acknowledges the signal for thrombocytopenia raised by the WHO. This event including other cell lines and pancytopenia are closely monitored. Bone marrow toxicity remains a potential risk for vemurafenib and is included in the Risk Management Plan (RMP) for the drug. The assessment of this event, as part of bicytopenia or pancytopenia in the context of bone marrow suppression is currently being investigated by Roche.

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The UMC Measures of Disproportionate Reporting

A brief guide to their interpretation

The Information Component (IC)

The Information Component (IC), originally introduced through the BCPNN (Bayesian Confidence Propagation Neural Network), is a measure of the disproportionality between the observed and the expected reporting of a drug-ADR pair. A positive IC value indicates that a particular drug-ADR pair is reported more often than expected, based on all the reports in the database. Similarly, a negative IC value means that the drug-ADR pair is reported less frequently than expected. The higher the value of the IC, the more the combination stands out from the background.

The IC value is solely calculated from:

- the total number of reports in the database (N_{tot})
- the total number of reports on the ADR term (N_{adr})
- the number of reports on the drug (N_{drug}), and
- the total number of reports on the specific drug-ADR pair (N_{comb}).

New reports may cause the IC to either increase or decrease. When the IC is calculated from large numbers, a new report is less likely to cause a major fluctuation in the IC value. The IC_{025} value is the lower limit of a 95% credibility interval for the IC. The credibility interval provides information about the stability of a particular IC value: the narrower the interval, the higher the stability.

The IC does not imply causality of a potential adverse reaction caused by a drug. The IC shows the quantitative dependency between the ADR and the drug based on the reporting to the WHO Global ICSR database.

If the IC value increases over time and the IC_{025} value is positive, this is suggestive of a connection between the drug and the adverse reaction. However, as alternative explanations for the positive IC need to be considered, clinical assessment remains essential in the identification of a signal.

Omega (Ω)

Omega (Ω) is, just as the IC, a measure of disproportionate reporting, however not for a drug-ADR pair but for a drug-drug-ADR triplet. The purpose of Ω is to detect potential signals of drug-drug interactions.

For Ω, the expected reporting on a drug-drug-ADR triplet is based on a model where both drugs add to the baseline risk of the ADR, independently of each other. A positive Ω indicates that the two drugs, when used together, increase the risk of the ADR more than the sum of the risks attributable to each drug separately.

Ω is calculated based on the following information:

- the relative reporting rate of the ADR for reports listing neither of the drugs (f_{00})
- the relative reporting rate of the ADR for reports listing drug 1 but not drug 2 (f_{10})
- the relative reporting rate of the ADR for reports listing drug 2 but not drug 1 (f_{01}), and
- the relative reporting rate of the ADR for reports listing both drugs (f_{11}).

As the IC, Ω may fluctuate over time as new reports enter the database. Also like the IC, each Ω comes with a 95% credibility interval, whose lower limit is denoted Ω_{025}. Ω does not imply causality of a potential drug-drug interaction. It is a quantitative measure of the deviation in reporting on the drug-drug-ADR triplet relative to a baseline model where the drugs are assumed to independently add to the baseline risk of the ADR.

If Ω increases over time and Ω_{025} is positive, this is suggestive of a drug-drug interaction, based on the reporting to the WHO Global ICSR database. However, as alternative explanations for the positive Ω need to be considered, clinical assessment of the case series is essential in the identification of an interaction signal.

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Caveat Document

Accompanying statement to data released from the WHO Collaborating Centre

Uppsala Monitoring Centre (UMC) in its role as the WHO Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring. Limited details about each suspected adverse reaction are received by the UMC. The information is stored in the WHO Global Individual Case Safety Report database, VigiBase. It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not.

Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Some National Centres strongly recommend that anyone who intends to use their information should contact them for interpretation.

Any publication, in whole or in part, of information obtained from UMC must include a statement:

(i) regarding the source of the information,
(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
(iii) that the information does not represent the opinion of the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

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