Signal

Tramadol and hyperacusis

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Summary

Tramadol and hyperacusis was identified as a potential signal in a screening of VigiBase, the WHO global database of individual case safety reports, focusing on patient reports. As of June 2019, there were 20 reports for the combination. Overall, they support an association between tramadol and hyperacusis with all cases reporting tramadol as the only suspect drug, and with a consistent time-to-onset of up to two days among all cases that provided it. In addition, six cases reported a positive dechallenge and two a positive rechallenge. κ-opioid receptor-mediated facilitation of NMDA receptor sensitivity to glutamate has been suggested as a mechanism for hyperacusis in rodents. Hyperacusis is not listed as an adverse reaction in the label for tramadol, and while changes in sensorial capacity is, this might not be specific enough for the patients, who would benefit from more precise labels.

Restricted

Introduction

Tramadol is indicated for the treatment of moderate to severe pain. It's an opioid agonist acting on μ-, δ- and κ-opioid receptors, with a higher affinity for the μ receptor.[1] The analgesic effect is also achieved by inhibiting neuronal reuptake of noradrenaline and by enhancing serotonin release. Peak plasma concentration is reached after 4.9 hours and the half-life is six hours.[1] The analgesic effect occurs within 30-60 minutes after intake.[2,3]

Hyperacusis can be described as experiencing "sounds of everyday life as intrusively loud, uncomfortable, and sometimes painful".[4] It can either develop suddenly or over time. To avoid noise, some people may withdraw from normal daily activities and may therefore become isolated. School and work may also be compromised.[4,5]

The causes of hyperacusis are unknown but it has been linked with a number of conditions including tinnitus, damage to the ear or brain, migraines, depression and post-traumatic stress disorder, Bell's palsy and Ménière's disease. Exposure to sudden loud noise or a negative life event can also trigger hyperacusis. However, for many people with hyperacusis there is no clear cause.[4,6]

Tramadol and hyperacusis was first identified as a potential signal in a screening of VigiBase focusing on patient reports, in April 2018. The aim of this assessment is to investigate if there is a causal correlation between tramadol and hyperacusis.

Reports in VigiBase

As of June 2019, there were 20 reports of tramadol and hyperacusis (see Table 1). The combination was not disproportionately over-reported, with the expected number of reports being 21 (26 June 2019). There were 15 cases for females and five for males. The reports came from Denmark (4), UK (4), Netherlands (4), Australia (2), US (2) and Canada, France, Norway, and Thailand (1 each). Age (given in 18 cases) ranged from 17 to 62 years, with a median of 38 years. Eleven reports were from consumers, four from pharmacists, four from physicians and the reporter type was unknown for the remaining.

In two cases, hyperacusis seemed to have occurred after tramadol withdrawal. In one case (5), the patient experienced hyperacusis, flu symptoms, tiredness, light sensitivity, poor sleep and formication after tramadol was stopped and the reporter attributed these to withdrawal symptoms. Another case (8) described a patient who was on tramadol treatment for five years for back pain (50 mg/d). The narrative revealed that six months after tramadol had been withdrawn the patient started treatment with sertraline and experienced extreme sound and light sensitivity, sexual dysfunction, extreme irritation/anger, suicidal thoughts, fatigue, and auditory hallucinations.

In all the remaining 18 cases, tramadol was the only drug reported as suspected. Concomitant drugs were reported in 10 cases, none of which are labelled for hyperacusis. Two cases (3, 17) reported the use of sumatriptan, which is used for migraines, and another case (4) reported the use of venlafaxine, which is usually used to treat depression. Both conditions have been linked with hyperacusis. Three cases (11, 18, 20) reported the use of other opioids in addition to tramadol.

Time-to-onset was provided in 14 cases and it was reported to be one day or less in 13; in the remaining case it was two days. The action taken with tramadol was unknown in six cases, dose not changed in four, dose reduced in one (case 11) and drug withdrawn in seven cases (cases 1, 2, 9, 12, 15, 17, 20). Of the eight cases where the drug was withdrawn or the dose was reduced, six reported a recovery. In case 15, concomitant drugs were also withdrawn at the same time as tramadol and the patient recovered. An additional four patients recovered but the action taken with the drug was either unknown or the dose was not changed.

Two cases (1, 18) reported a positive rechallenge. Case 18, reported by a physician, described a 32-year-old patient who experienced hyperacusis (no other events reported) on the same day that treatment with tramadol was started. The case reported a positive rechallenge but there was no detailed information about the event, and it did not state whether the drug was withdrawn, prior to rechallenge. Case 1 described a patient who experienced hyperacusis 15-25 minutes after starting on tramadol for postoperative pain. No other concomitant drugs and no other adverse events were reported. Both a positive dechallenge and a positive rechallenge were reported (without much information about the event).

A few cases illustrate how hyperacusis affected the patient's life. For example, case 3 described a 32-year-old female who experienced increased sound sensitivity only when taking tramadol, which went away once the dose wore off. The patient also took desogestrel/ethinylestradiol, levothyroxine and sumatriptan:

> *"Sounds become louder, more penetrating and grating. For example, when someone is talking or cutlery on a plate. Almost like sound is more in your face. It becomes difficult to be around other people or in noisy places."*

Twelve cases co-reported other reactions. The top co-reported terms were headache (6 cases), nausea (5), dizziness (4), photophobia (4), somnolence (4), vomiting (4), fatigue (3), hyperhidrosis (3), insomnia (3) and irritability (3). All of these are labelled in the tramadol Summary of Product Characteristics (SmPC) except for photophobia and irritability.[1]

Literature and Labelling

Hyperacusis is not labelled for tramadol in either the UK or the US.[1,7] However, tinnitus is described as a symptom of withdrawal in the UK SmPC,[1] along with psychiatric adverse reactions, including changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase), and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders). In the US label, tinnitus and deafness are listed under "other adverse experiences, causal relationship unknown".[7]

Hyperacusis is not given on the Patient Information Leaflet (PIL) either. However some PILs for different tramadol products state that psychological reactions may appear, such as "a change in mood (mostly high spirits, occasionally irritated mood), changes in activity (slowing down but sometimes an increase in activity), and decreased cognitive and sensory perception (being less aware and less able to make decisions, which may lead to errors in judgement)".[8,9] The PIL for another product lists "changes in senses and recognition" as an adverse reaction.[10]

The SmPCs for the opioid oxycodone, list hyperacusis as an adverse reaction.[11,12] Some brands list it under the group "ear and labyrinth disorders", while others list it under "psychiatric disorders".

In the PIL, "abnormally acute sense of hearing (hyperacusis)" is described.[13] However, the labels for other opioids such as morphine, codeine, tapentadol, hydromorphone, hydrocodone, fentanyl, buprenorphine, oxymorphone, meperidine, methadone, pentazocine, and butorphanol do not list hyperacusis, while labels for buprenorphine, butorphanol and fentanyl list tinnitus.[14-16]

Discussion

It has been suggested that opioids can affect hearing. There have been reports of hearing loss associated with chronic opioid use or with opioid overdose.[17,18] Also, as mentioned above, tinnitus (even deafness) is listed in the labels of some opioids including tramadol.[1,7,14-16] Often, tinnitus and hyperacusis co-exist. In patients with a primary complaint of hyperacusis, the prevalence of tinnitus has been reported to be 86%. For patients with a primary complaint of tinnitus, the prevalence of hyperacusis has been reported to be 40%. As such it has been suggested that hyperacusis and tinnitus could have common mechanisms.[19]

Both hyperacusis and tinnitus can be worsened by fatigue and stress. In their work, Sahley et al. proposed that in response to stress, endogenous dynorphins are released that act on κ-opioid receptors in cochlea.[20,21] This in turn might facilitate NMDA receptor sensitivity to glutamate, possibly leading to increased auditory sensitivity. Indeed in one of their studies, κ-opioid receptor agonists ((-) pentazocine and U-50488H) were administered across the cochlear round window membrane in chinchillas.[20] The amplitude changes observed amounted to increases in sensitivity of between 4 to 8 decibels. So a suggested mechanism for hyperacusis is through κ-opioid receptor-mediated facilitation of NMDA receptor sensitivity to glutamate, that may occur under stressful conditions.[21]

As previously mentioned, oxycodone is labelled for hyperacusis.[11,12] A study found that oxycodone acts as a κ_{2b}-opioid agonist with relatively low affinity for the μ receptor.[22] This could strengthen the hypothesis that hyperacusis could be mediated by κ-opioid receptor activation. On the other hand, tramadol has the highest affinity for the μ receptor.[1,23] However, it still acts on κ receptors and could in theory also cause hyperacusis through them, but perhaps to a lesser extent.

Considering the extensive use of tramadol globally, the number of reports in VigiBase is low. The association is not disproportionally over-reported, with the number of observed reports being 20 and the expected number 21. However, the available cases do support a relationship between tramadol intake and hyperacusis. Specifically, all cases reported tramadol as the only suspect drug and the time-to-onset was two days or less among the 14 cases that provided it. Also, in the eight cases where tramadol was withdrawn or its dose reduced, six reported a positive dechallenge and two a positive rechallenge.

A few cases mentioned other conditions linked with hyperacusis. Two (3, 17) reported concomitant treatment with sumatriptan, which is used for migraines. But in both of these, hyperacusis occurred on the same day as tramadol was started. Also, in case 17, the patient had been on sumatriptan for 12 years before tramadol introduction, so the patient's history of migraines seems unlikely to be related to the event. The start date of sumatriptan in case 3 was unknown. Another case (4) reported treatment with venlafaxine for an "ill-defined disorder". The drug is usually used to treat depression, also a condition to which hyperacusis has been linked. However, the start date of both venlafaxine and tramadol was not given and thus the time relationship to the event is unknown.

Moreover, three cases reported the use of another opioid in addition to tramadol. Cases 11 and 18 report codeine/paracetamol with unknown start date, but in both cases hyperacusis occurred within one day after the start of tramadol. Case 20 mentions concomitant treatment with pentazocine which has agonist action at κ-opioid receptors and antagonist action at μ receptors.[24] Pentazocine was started a week before and stopped a day before tramadol was introduced and hyperacusis occurred.

One could argue that the adverse reaction "changes in sensorial capacity" or "changes in senses and recognition" described in tramadol labels[1,10] could be interpreted as encompassing changes in hearing capacity, e.g. hyperacusis, since hearing is one of the five basic senses in humans (sight, hearing, taste, smell, touch). However, patients might not realise that hyperacusis could be part of this and the majority of these reports come from consumers.

Conclusion

Hyperacusis following the intake of tramadol has been found in VigiBase from a number of countries. The association is not disproportionally over-reported. However, the following point towards a causal relationship:

- Tramadol is the only suspected drug in all cases.
- There is a close temporal relationship (two days or less) when the information on time-to-onset is available.
- Six cases report a positive dechallenge and two also report a positive rechallenge although details in some reports were missing.
- κ-opioid receptor-mediated facilitation of NMDA receptor sensitivity to glutamate has been suggested as a mechanism for hyperacusis.
- The opioid oxycodone is labelled for hyperacusis.

The label for tramadol already lists changes in sensorial capacity as an adverse reaction. However, patients may not realise that hyperacusis could be part of this and may not appreciate the possible impact it could have on the quality of life. Since the majority of these reports come from consumers, they could benefit from clearer labels.

References

1. Electronic Medicines Compendium: Summary of Product Characteristics for tramadol (Brimisol®). Available from: https://www.medicines.org.uk/emc/product/8550/smpc. Accessed: 15 June 2019.

2. Tramadol: strong painkiller to treat severe pain. nhs.uk. 2018. Available from: https://www.nhs.uk/medicines/tramadol/. Accessed: 5 Dec 2019.

3. Tramadol Hydrochloride Monograph for Professionals - Drugs.com. Available from: https://www.drugs.com/monograph/tramadol-hydrochloride.html. Accessed: 5 Dec 2019.

4. Hyperacusis. British Tinnitus Association. Available from: https://www.tinnitus.org.uk/hyperacusis. Accessed: 5 Dec 2019.

5. What Causes This? | Hyperacusis. Available from: http://www.hyperacusis.net/what-is-it/what-causes-this/. Accessed: 5 Dec 2019.

6. What Is Sound Sensitivity (Hyperacusis)? WebMD. Available from: https://www.webmd.com/brain/sound-sensitivity-hyperacusis. Accessed: 5 Dec 2019.

7. US Food and Drug Administration: Product label for tramadol. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ae7c54b1-b440-4cca-97e8-e5b825413d32&audience=consumer. Accessed: 6 Sep 2019.

8. Electronic Medicines Compendium: Patient Information Leaflet for tramadol (Maxitram SR®). Available from: https://www.medicines.org.uk/emc/product/6989/pil. Accessed: 9 Oct 2019.

9. Electronic Medicines Compendium: Patient Information Leaflet for tramadol (Maneo®). Available from: https://www.medicines.org.uk/emc/product/8475/pil. Accessed: 4 Nov 2019.

10. Electronic Medicines Compendium: Patient Information Leaflet for tramadol. Available from: https://www.medicines.org.uk/emc/product/4648/pil. Accessed: 4 Nov 2019.

11. Electronic Medicines Compendium: Summary of Product Characteristics for oxycodone (Carexil®). Available from: https://www.medicines.org.uk/emc/product/2068/smpc. Accessed: 9 Oct 2019.

12. Electronic Medicines Compendium: Summary of Product Characteristics for oxycodone (Lynlor®). Available from: https://www.medicines.org.uk/emc/product/1197/smpc. Accessed: 31 Oct 2019.

13. Electronic Medicines Compendium: Patient Information Leaflet for oxycodone (Lynlor®). Available from: https://www.medicines.org.uk/emc/product/1197/pil. Accessed: 31 Oct 2019.

14. Electronic Medicines Compendium: Summary of Product Characteristics for buprenorphine (Bunov®). Available from: https://www.medicines.org.uk/emc/product/9798/smpc. Accessed: 22 Jul 2019.

15. US Food and Drug Administration: Product label for butorphanol. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b8e48063-0b40-ee43-85c1-4ef2de80c404&audience=consumer. Accessed: 22 Jul 2019.

16. Electronic Medicines Compendium: Summary of Product Characteristics for fentanyl. Available from: https://www.medicines.org.uk/emc/product/5400/smpc. 22 Jul 2019.

17. Oroei M, Peyvandi AA, Mokhtarinejad F. Opioid Drugs and Sensorineural Hearing Loss. Addict Health. 2018 Jan;10(1):64–6.

18. Kopec KT, Nelson LS. Opioid-Induced Hearing Loss. Emergency Medicine. 2012 Nov;44(11):4–6.

19. Baguley DM. Hyperacusis. J R Soc Med. 2003 Dec;96(12):582–5.

20. Sahley TL, Anderson DJ, Chernicky CL. Bi-phasic intensity-dependent opioid-mediated neural amplitude changes in the chinchilla cochlea: partial blockade by an N-Methyl-D-Aspartate (NMDA)-receptor antagonist. Eur J Pharmacol. 2008 Feb 2;580(1–2):100–15.

21. Sahley TL, Hammonds MD, Musiek FE. Endogenous dynorphins, glutamate and N-methyl-d-aspartate (NMDA) receptors may participate in a stress-mediated Type-I auditory neural exacerbation of tinnitus. Brain Res. 2013 Mar 7;1499:80–108.

22. Nielsen CK, Ross FB, Lotfipour S, Saini KS, Edwards SR, Smith MT. Oxycodone and morphine have distinctly different pharmacological profiles: radioligand binding and behavioural studies in two rat models of neuropathic pain. Pain. 2007 Dec 5;132(3):289–300.

23. Raffa B, Vaught L, Shank P, Codd E. Opioid and Nonopioid Components Independently Contribute to the Mechanism of Action of Tramadol, an 'Atypical' Opioid Analgesic. 1992;260:11.

24. Electronic Medicines Compendium: Summary of Product Characteristics for pentazocine. Available from: https://www.medicines.org.uk/emc/product/8833/smpc. Accessed. 11 Nov 2019.

Table 1. Characteristics of case reports in VigiBase of hyperacusis in association with tramadol.

Case number	Age/ Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA PT)	Time-to-onset (TTO)	Action taken with drug (dechallenge/ rechallenge, - for unknown)	Outcome
1	-/F	Tramadol (S)	Hyperacusis	15-25 minutes	Drug withdrawn/ Reaction abated Rechallenge/ Reaction recurred Note: no details around rechallenge – only reported in structured field	Recovered
2	38/F	Tramadol (S) Acetylsalicylic acid, Gabapentin, Macrogol 3350, Senna (C)	Dyspnoea, Flushing, Hyperacusis, Hypopnoea, Somnolence	- Note: TTO not reported but narrative reveals that events occurred after tramadol intake and the duration of tramadol use was 1 day.	Drug withdrawn/-	Unknown
3	32/F	Tramadol (S) Desogestrel/ ethinylestradiol, Levothyroxine, Sumatriptan (C)	Hyperacusis	0 days	Dose not changed/-	Unknown
4	-/F	Tramadol (S), Venlafaxine (C)	Asthenia, Decreased appetite, Fatigue, Hyperacusis, Irritability, Malaise, Tinnitus	-	Dose not changed/ No effect observed	Not recovered
5	54/F	Tramadol (S)	Fatigue, Formication, Hyperacusis, Influenza, Photophobia, Poor quality sleep, Withdrawal syndrome	- Note: Patient had been on tramadol for years and experienced ADRs in response to drug withdrawal.	-/Reaction abated	Recovering

Case number	Age/ Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA PT)	Time-to-onset (TTO)	Action taken with drug (dechallenge/ rechallenge, - for unknown)	Outcome
6	21/M	Tramadol (S) Note: follow-up information also reveals treatment with "THC"	Abdominal pain upper, Aggression, Anxiety, Appetite disorder, Bone pain, Burning sensation, Confusional state, Constipation, Coordination abnormal, Decreased immune responsiveness, Dependence, Depression, Disturbance in attention, Dizziness, Dry mouth, Dysgeusia, Erectile dysfunction, Euphoric mood, Fatigue, Feeling hot, Gastric ulcer, Headache, Heart rate decreased, Hyperacusis, Hyperaesthesia, Hyperhidrosis, Hypoglycaemia, Influenza like illness, Insomnia, Irritability, Memory impairment, Mental impairment, Muscle spasms, Muscle twitching, Nausea, Neuralgia, Orthostatic hypotension, Paraesthesia, Parosmia, Periodontitis, Photophobia, Pyrexia, Shock, Somnolence, Syncope, Throat tightness, Vision blurred, Vomiting, Weight fluctuation, Withdrawal syndrome	0 days	-	Not recovered
7	41/F	Tramadol (S)	Hyperacusis, Insomnia, Pruritus	0 days	-/Reaction abated	Recovered
8	40/M	Tramadol (S)	Anxiety, Cognitive disorder, Derealisation, Fatigue, General physical health deterioration, Hyperacusis, Impaired work ability, Memory impairment, Nervous system disorder, Photophobia, Psychotic disorder	- Note: Patient had used tramadol for 5 years. 6 months after stopping treatment with tramadol patient was treated with sertraline to which he experienced sound sensitivity among other reactions	-/Reaction abated	Recovered

Case number	Age/ Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA PT)	Time-to-onset (TTO)	Action taken with drug (dechallenge/ rechallenge, - for unknown)	Outcome
9	20/F	Tramadol (S)	Hyperacusis	4 hours	Drug withdrawn/ Reaction abated	Recovered
10	20/F	Tramadol (S)	Hyperacusis	30 minutes	Dose not changed/ Reaction abated	Recovered
11	28/F	Tramadol (S) Codeine/paracetamol (C)	Aggression, Amnesia, Anger, Anxiety, Confusional state, Delusion, Depressed mood, Emotional disorder, Feeling abnormal, Hallucination, Headache, Hyperacusis, Irritability, Pain, Photophobia, Somnolence, Tremor	1 day (within)	Dose reduced/No effect observed	Not recovered
12	57/F	Tramadol (S)	Dizziness, Feeling abnormal, Headache, Hyperacusis, Photophobia, Somnolence	- Note: TTO not reported but tramadol was stopped the same day it was started.	Drug withdrawn/ Reaction abated	-
13	17/F	Tramadol (S), Paracetamol (C)	Hyperacusis	2 days	Dose not changed/-	Unknown
14	47/F	Tramadol (S)	Asthenia, Feeling cold, Headache, Hyperacusis, Hyperhidrosis, Syncope, Tremor	-	-	-
15	38/F	Tramadol (S), Diclofenac, Tolperisone (C)	Hyperacusis, Nausea, Rash, Vomiting	0 days	Drug withdrawn/ Reaction abated Note: concomitant drugs also reported to be withdrawn on same day as tramadol	Recovered
16	62/M	Tramadol (S), Atenolol, Ibuprofen (C)	Disturbance in attention, Dysarthria, Hyperacusis, Nausea, Panic attack, Urinary retention, Vomiting	2 hours Note: ibuprofen was introduced at the same time as tramadol.	Drug withdrawn/-	-
17	39/M	Tramadol (S), Paracetamol, Sumatriptan, Testosterone (C) Note: concomitant drugs had been taken for 12-23 years before tramadol introduction.	Anorgasmia, Constipation, Dizziness, Dry mouth, Fatigue, Headache, Hyperacusis, Hyperhidrosis, Insomnia, Logorrhoea, Nausea, Pruritus, Respiratory rate decreased, Tremor	1 hour	Drug withdrawn/ Reaction abated	Recovered

Case number	Age/ Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA PT)	Time-to-onset (TTO)	Action taken with drug (dechallenge/ rechallenge, - for unknown)	Outcome
18	32/F	Tramadol (S) Bupivacaine/glucose, Codeine/paracetamol, Diclofenac, Paracetamol, Rubella vaccine (C)	Hyperacusis	0 days	- Rechallenge/ Reaction recurred Note: withdrawal information lacking although a positive rechallenge is reported	Recovered
19	51/F	Tramadol (S)	Balance disorder, Headache, Hyperacusis, Photophobia, Vomiting	1 day	-	Recovered
20	36/M	Tramadol (S) Bendroflumethiazide/ propranolol, Diazepam, Pentazocine (C)	Decreased appetite, Dizziness, Hyperacusis, Nausea, Stomatitis	0 days	Drug withdrawn Note: pentazocine, another opioid with agonist action at kappa receptors, was started a week before and stopped a day before tramadol was started and subsequent onset of ADR. Tramadol was withdrawn a day after reaction occurred. It is possible that pentazocine could be related to event.	Recovering

SIGNAL

WHO defines 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 states: "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 supporting 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 as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

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

Responses from industry

Signals on products under patent are submitted to patent holders for comments. 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.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (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 Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: 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 is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: 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 adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

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

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

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

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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