Signal

Colecalciferol and insomnia

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Summary

Colecalciferol (vitamin D_3) is a steroid hormone mainly used for prophylaxis and treatment of vitamin D deficiency in elderly women and young children. Insomnia, defined as a disruption in the amount and quality of sleep that impairs functioning, is a major health issue affecting 50% of all people occasionally and 10-20% chronically. During a joint UMC/Lareb signal detection sprint with a focus on patient reports, the MedDRA preferred term 'insomnia' was highlighted for the drug colecalciferol in VigiBase, the WHO global database of individual case safety reports. As of 11 December 2018, there were 52 reports for this drug–adverse drug reaction combination. The majority of the reports had co-reported drugs and/or reactions that may have contributed to the insomnia, but there were a few well documented cases that point to a possible causal association of colecalciferol and insomnia. In 21 cases the reaction abated when the drug was withdrawn and in seven the reaction recurred when the drug was readministered. A few reports also indicate a dose relationship since the reaction subsided when the dose was reduced. Insomnia is not labelled for colecalciferol and there are no case reports in the scientific literature to support a causal link. However, there is growing evidence that vitamin D may play a role in sleep regulation, influencing both sleep quantity and quality, although the mechanism of action by which vitamin D regulates sleep is not well understood and needs further investigation.

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Introduction

Colecalciferol (vitamin D_3) is a steroid hormone used for the prophylaxis and treatment of vitamin D deficiency and as an adjunct to osteoporosis therapy. The drug is taken by both children and adults, with young children and the elderly (mainly women) being the main target groups. Vitamin D deficiency in children can have adverse health consequences, such as growth failure and rickets, and vitamin D supplementation for infants is therefore common in countries where a lack of sunlight may cause this. On the other hand, individual tolerance to vitamin D varies considerably (infants and children are generally more sensitive) and the difference between a therapeutic or a toxic concentration is relatively small.[1]

Colecalciferol is the natural precursor of the calcium-regulating hormone calcitriol, and has an important role in regulating body levels of calcium and phosphate in bone formation and bone resorption. It is produced in the skin under the influence of UV radiation, promotes calcium uptake in the small intestine and stimulates phosphate transport. It inhibits the excretion of calcium and phosphate in the kidney by promoting tubular resorption and inhibits the production of parathyroid hormone (PTH) in the parathyroids. Colecalciferol is often combined with calcium. Adverse events are generally associated with excessive intake of colecalciferol leading to hypercalcaemia.

Insomnia is defined as a disruption in the amount and quality of sleep that impairs functioning (or the subjective experience of insufficient sleep). It is a major health problem, affecting 50% of all people occasionally and 10-20% chronically.[2] Chronic insomnia can affect the ability to undertake tasks such as going to work or school. Insomnia is more common in women than in men. Older women are at a higher risk of insomnia, potentially due to hormonal changes.[3] Primary insomnia occurs in the absence of underlying diseases or conditions and is not as common as secondary insomnia that can be related to a cause, e.g. drug use, mood disorders, restless legs syndrome, sleep apnoea, or travel across time zones.[2] There are several patient forums and personal blogs where the link between vitamin D intake and insomnia has been proposed and discussed.

Many classes of drugs are known to cause sleep disturbances, e.g. alpha- and beta blockers, corticosteroids, selective serotonin reuptake inhibitor (SSRI) antidepressants, angiotensin-converting enzyme (ACE) inhibitors, benzodiazepines, barbiturates, and opioids.

Reports in VigiBase

During a joint UMC/Lareb signal detection sprint, held in October 2016, with a focus on patient reports, the MedDRA preferred term 'insomnia' was highlighted for the drug colecalciferol in VigiBase, the WHO global database of individual case safety reports (ICSRs). The combination was deemed eligible for in-depth assessment in 2018 after having been kept under review for some time to see if more informative cases would strengthen the potential signal. As of 11 December 2018, there were 52 reports for this drug–adverse drug reaction (ADR) combination in VigiBase. Based on the overall reporting of adverse reactions for colecalciferol, and of the adverse reaction insomnia in VigiBase, the expected value for the number of reports on the combination was 38, and the association was highlighted as disproportionally reported, by IC analysis.[4]

The reports came from 18 countries across four continents; Europe (37 reports), the Americas (12), Asia (2), and Africa (1). More female than male patients were affected (75% women) and the age range was between nine days old and 79 years, with a median of 51 years. Consumers/non-healthcare professionals accounted for 73% of the reports of which 33% were serious. In 24 cases, colecalciferol was the only reported drug and in 34 cases it was the only suspected drug. The most frequently co-reported drugs were levothyroxine (5 cases), which may also cause insomnia, hydrocodone/paracetamol (4), and lisinopril (4). In a few cases the insomnia had been suspected to be caused by drug interactions.

Most co-reported reactions were anxiety (10 cases), irritability (9), abdominal pain (8), dizziness (8) and nausea (7), and there were quite a few cases where various gastrointestinal reactions, skin reactions and restlessness were co-reported. These co-reported reactions may have contributed to the insomnia. Seven cases concerned infants where colic seems to have been the primary ADR and an indirect cause of insomnia. In a handful of cases, the patient seems to have suffered from allergic reactions with many symptoms, and in two of these cases, the excipients brilliant blue (colouring agent) and mannitol were suspected. One patient had a medical history of sleep apnoea which is a risk factor for insomnia.

The vast majority of the patients were administered colecalciferol due to a vitamin D deficiency or as prophylaxis, and the dose varied to a great extent. The time to onset was reported in 26 cases, ranging from 30 seconds to five months, with a median of 2.5 days, but in 46% of these cases the reaction occurred within a day. In 21 cases the reaction abated when the drug was withdrawn, and in seven the reaction recurred when the drug was readministered.

A selection of well documented reports is presented in Table 1. Case 1 concerns an infant who was given colecalciferol drops as a vitamin supplement on two consecutive days and suffered from insomnia following each administration. The ADR resolved spontaneously after stopping the drug. No other drugs were given to the infant and no other health problem was reported.

In Case 2 an 8-year-old girl experienced sleeplessness, dizziness and excessive drinking [as in increased thirst red.] five days after taking an oral dose of colecalciferol. At the time of reporting, 11 days after the drug had been withdrawn, the patient was recovering. She had no known related medical history or concomitant medication. However, although the dose stated in the report was within the normal range, this may be a case of overdosage since the symptoms included thirst and vertigo.[1]

Case 3 describes a 79-year-old patient who, according to the primary source, "felt mind alive and infinite unable to sleep" three days after taking colecalciferol orally. Warfarin, alendronic acid and folic acid were listed as concomitant without start dates so it's reasonable to believe that the patient had been taking those for some time already. The drug was withdrawn and the insomnia disappeared but a week later the patient took another dose of the drug, the reaction recurred and the drug was withdrawn again.

Case 4 concerns a 49-year-old patient who was unable to sleep six hours after taking an oral dose of colecalciferol. The patient was recovering when the dose was reduced. The drug quetiapine, for which somnolence is labelled as an adverse effect, was listed as concomitant. However, it usually occurs during the first two weeks of treatment and then disappears, and the patient had been on quetiapine for four years. The patient had no related medical history nor past drug therapy.

Case 5 presents a 56-year-old patient with osteoporosis who started taking weekly doses of oral colecalciferol in December and suffered from insomnia, irritability and restlessness in early January. The drug was withdrawn and the reaction abated. Six weeks later, the drug was readministered with the same outcome. The dose was then reduced, the ADR subsided and the lower dose was well tolerated.

Table 1. Characteristics of a selection of well documented case reports in VigiBase of insomnia in association with colecalciferol

Case	Reporter	Age/Sex	Suspected (S) or concomitant (C) drugs	Reactions (WHO-ART preferred terms)	Time to onset	Action taken
1	Pharmacist	6 months/F	Colecalciferol (S)	Insomnia	0 days	Drug withdrawn, reaction abated Drug readministered, reaction recurred
2	Consumer	8/F	Colecalciferol (S)	Sleeplessness, dizziness, excessive drinking	5 days	Drug withdrawn, reactions abated
3	Physician	79/F	Colecalciferol (S) Warfarin (C) Alendronic acid (C) Folic acid (C)	Insomnia	3 days	Drug withdrawn, reaction abated Drug readministered, reaction recurred
4	Consumer	49/F	Colecalciferol (S) Quetiapine (C)	Insomnia	6 hours	Dose reduced, reaction abated
5	Pharmacist	56/F	Colecalciferol (S)	Insomnia, irritability, restlessness	A few weeks	Drug withdrawn, reactions abated Drug readministered, reactions recurred Dose reduced, reactions abated

Literature and Labelling

Insomnia is not labelled for colecalciferol in the most recent Summary of Product Characteristics (SPC) in the United Kingdom[5] and there are no case reports in the scientific literature to support a causal link. However, there are studies which propose a connection between vitamin D and sleep regulation. Colecalciferol is a steroid hormone, and hormones are involved in the regulation of the sleep-wake cycle.[6] Furthermore, colecalciferol regulates the body levels of calcium and the symptoms of hypercalcaemia can include somnolence.[1]

Several studies have investigated the potential link between vitamin D deficiency and sleep disorders, and there is growing evidence that vitamin D may play a role in sleep regulation, influencing both sleep quantity and quality.[7,8] In one study, researchers analysed the sleep patterns and vitamin D levels among a group of older adult men and found that vitamin D deficiency was associated with less sleep overall and more disrupted sleep.[9] A study on Chinese schoolchildren concluded that low levels of vitamin D were associated with the risk of insufficient sleep.[10] This could indicate confounding by indication.

The mechanism of action by which vitamin D regulates sleep is not well understood. According to a recent review article, vitamin D binds to receptors in areas of the brainstem involved in sleep regulation. Cells in these areas play an important role in the first stages of sleep and in sleep maintenance. The enzymes controlling vitamin D activation and degradation are also expressed in the brain. Furthermore, vitamin D plays a pivotal role in the synthesis of melatonin, the pineal hormone controlling human circadian rhythms and sleep.[8] Vitamin D has also been shown to regulate the synthesis of a variety of neurotransmitters, including serotonin and dopamine, which are known to promote waking and inhibit sleep.[11,12] Dopamine can inhibit the production and release of melatonin.[13]

Discussion and Conclusion

The majority of the reports have co-reported drugs and/or reactions that may have contributed to the insomnia, and, as stated above, low levels of vitamin D may also affect sleep and be a potential explanation for insomnia. However, case reports in VigiBase point to a possible causal association of colecalciferol and insomnia. The 52 reports came from 18 countries, and colecalciferol was the only suspected drug in 34 cases. Of the 26 reports where a time to onset was specified, 12 patients experienced the reaction insomnia within a day. In 21 cases the reaction abated when the drug was withdrawn and in seven cases the reaction recurred when the drug was readministered. A few reports also indicate a dose relationship since the reaction subsided when the dose was reduced.

Among the better documented cases shown in the table, the first one, concerned an infant where no reactions other than insomnia were reported, but in all other cases concerning infants, reactions such as abdominal pain/infant colic and/or crying were co-reported. In the second selected case, the patient was a child who in addition to insomnia suffered from dizziness and increased thirst, symptoms which may indicate overdosage, particularly since the risk of toxicity is greater among children. Cases 3 and 4 have concomitant drugs, but they are unlikely to have caused the insomnia; in both cases, insomnia was the only reported reaction. For the patient in the third case, the reaction abated when the drug was withdrawn and recurred about a week later when the drug was readministered. In the fourth case, the reaction abated when the dose of colecalciferol was reduced. In the last case, colecalciferol was the only reported drug. The co-reported reactions irritability and restlessness may have contributed to the insomnia, but all reactions abated when the drug was withdrawn, recurred upon readministration, and subsided when the dose was reduced. There is thus a strong case for a causal relationship.

VigiBase case reports and studies suggest a link between vitamin D and sleep disturbances, but further investigations are needed to determine the exact mechanism of action.

References

1. Medicines Complete: Adverse effects and treatment for colecalciferol. Available from: https://www.medicinescomplete.com/#/content/martindale/7892. Accessed: 25 Mar 2019.

2. Taber's Online Medical Dictionary: Search term 'insomnia'. Available from: https://www.tabers.com/tabersonline. Accessed: 25 Mar 2019.

3. Office on women's health: Search term 'insomnia'. Available from: https://www.womenshealth.gov/a-z-topics/insomnia. Accessed: 7 May 2019.

4. Norén GN, Hopstadius J, Bate A. Shrinkage Observed-to-expected Ratios for Robust and Transparent Large-scale Pattern Discovery. Stat Methods Med Res. 2013 Feb 1;22(1):57-69.

5. Electronic Medicines Compendium: Summary of Product Characteristics for colecalciferol (Desunin®) Available from: https://www.medicines.org.uk/emc/product/7263/smpc. Accessed: 25 March 2019.

6. Terán-Pérez G, Arana-Lechuga Y, Esqueda-León E, Santana-Miranda R, Rojas-Zamorano JÁ, Velázquez Moctezuma J. Steroid Hormones and Sleep Regulation. Mini Rev Med Chem. 2012 Oct;12(11):1040-8.

7. Gao Q, Kou T, Zhuang B, Ren Y, Dong X, Wang Q. The Association between Vitamin D Deficiency and Sleep Disorders: A Systematic Review and Meta-Analysis. Nutrients. 2018 Oct 1;10(10):1395.

8. Muscogiuri G, Barrea L, Scannapieco M, Di Somma C, Scacchi M, Aimaretti G, et al. The lullaby of the sun: the role of vitamin D in sleep disturbance. Sleep Med. 2019 Feb 1;54:262-5.

9. Massa J, Stone KL, Wei EK, Harrison SL, Barrett-Connor E, Lane NE, et al. Vitamin D and Actigraphic Sleep Outcomes in Older Community-dwelling Men: the MrOS Sleep Study. Sleep. 2015 Feb 1;38(2):251–7.

10. Gong QH, Li SX, Li H, Chen Q, Li XY, Xu GZ. 25-Hydroxyvitamin D Status and Its Association with Sleep Duration in Chinese Schoolchildren. Nutrients. 2018 Aug 3;10(8):1013.

11. Jiang P, Zhang LH, Cai HL, Li HD, Liu YP, Tang MM, et al. Neurochemical Effects of Chronic Administration of Calcitriol in Rats. Nutrients. 2014; 6(12):6048-59.

12. Monti JM, Jantos H. The Roles of Dopamine and Serotonin, and of Their Receptors, in Regulating Sleep and Waking. Prog Brain Res. 2008; 172:625-46.

13. González S, Moreno-Delgado D, Moreno E, Pérez-Capote K, Franco R, Mallol J, et al. (2012) Circadian-Related Heteromerization of Adrenergic and Dopamine D4 Receptors Modulates Melatonin Synthesis and Release in the Pineal Gland. PLoS Biol. 2012;10(6).

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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