Signal

Repeated capsaicin exposure leading to severe and possibly chronic hypersensitivity

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Summary

In a screening of VigiBase, the WHO global database of individual case safety reports, a case series was identified describing individuals who experienced hypersensitivity reactions due to capsaicin exposure. Many of the reported reactions are listed in product labels and prescribing information for capsaicin. However, our case series reveals that some of the experienced reactions are more severe than what is depicted in the labels. In addition, the reactions, even if starting out mild, could become more severe and even chronic with repeated exposure. Nurses and other health care professionals (HCPs) administering capsaicin treatments could be especially vulnerable, due to more frequent exposure, despite adhering to the recommended protective measures that exist for HCPs.

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Introduction

Capsaicin is the compound found in chili peppers that causes the heat and burning sensation we feel when consuming them.[1] As well as its culinary uses, capsaicin can be used to treat pain. The specific indications vary with the product but include treatment of peripheral neuropathic pain, post-herpetic neuralgia, and symptomatic management of painful diabetic peripheral polyneuropathy.[2, 3] Capsaicin is an agonist for the transient receptor potential vanilloid 1 (TRPV1) receptor. The initial effect of capsaicin is the activation of TRPV1-expressing cutaneous nociceptors, which can cause pain, pungency and erythema.[1, 2] Later effects include desensitization of cutaneous nociceptors, which is thought to underlie the pain relief.

Adverse reactions described in the label for the capsaicin patch (Qutenza), include burning sensation, dysgeusia, hypoesthesia, eye irritation, palpitations, throat irritation, cough, pruritis, nausea, increased blood pressure, and application site reactions (burning, pain, erythema, pruritis, swelling).[2] For the cream formulation, runny eyes and sneezing are also listed[3]; in addition, for the cream it is noted that there have been a few reports of dyspnoea, wheezing and exacerbation of asthma. In the Qutenza prescribing information, nasopharyngitis, bronchitis and sinusitis are also given.[4] Hypersensitivity to capsaicin is a contraindication.[2, 3]

In the labels, precautions to be taken when handling the capsaicin patch, are also listed. Firstly, the patch should be administered by a physician or by a health care professional (HCP) under the supervision of a physician.[2] When handling the patch, nitrile gloves should always be worn; a mask and protective glasses are recommended. Patches should not be held near eyes or mucous membranes. Removal should be done gently and slowly by rolling the patch inward to minimize the risk of aerosolization of capsaicin and thus avoid exposure through inhalation. It is also advised to perform treatment in a well-ventilated area.

The combination of capsaicin and hypersensitivity was first identified in a screening of VigiBase, the WHO global database of individual case safety reports, focusing on reports indicating severe reactions[5], in December 2018. In a preliminary assessment of the cases it was observed that for some reports, the reaction experienced, although often labelled, seemed more severe than what was depicted in product labels. It was also noticed that nurses experienced these reactions while giving the treatment, and that repeated exposure might worsen the reactions. It was therefore decided to also look at cases reporting the term *occupational exposure to product*.

Reports in VigiBase

Characteristics of reports

As of 31 January 2020, there were 42 capsaicin cases in VigiBase reporting the MedDRA preferred term (PT) *Hypersensitivity*, the expected number of reports being 16 (IC_{025} = 0.9; 17 February 2020). For the PT *Occupational exposure to product* there were 105 cases compared to the expected 0 (IC_{025} = 7.0). Seven cases reported both terms. The cases came from the United States of America and countries in Europe, including the Czech Republic, Denmark, Finland, France, Germany, the Netherlands, Norway, Portugal, Spain, Sweden and the United Kingdom.

Of the hypersensitivity cases, women comprised 76% of them and men 12%; the rest were unknown. The age ranged between 27 and 84 years, the median being 54 years. The capsaicin patch was the most commonly used formulation (62%). Serious cases constituted 52% of the reports. The top 10 co-reported reactions were cough (10 cases), throat irritation (9), occupational exposure to product (7), dyspnoea (5), pruritis (5), application site pain (4), eye pain (4), urticaria (4), application site erythema (3), and blister (3).

Of the occupational exposure cases, women made up 93% while men only accounted for 4%, which might reflect a higher number of female nurses. The sex was unknown for the rest. The age ranged between 27 and 65 years, with the median being 47 years. The capsaicin patch was also the most used formulation (96%) among these cases. Serious cases made up 12% of the reports. The top 10 co-reported reactions were throat irritation (44 cases), cough (35), dyspnoea (23), eye irritation (14), eye pain (9), wrong technique in product usage process (8), glossitis (7), hypersensitivity (7), rhinorrhoea (7), and rhinalgia (7).

The co-reported reactions for both terms overlap and mainly describe symptoms of hypersensitivity of which many are known for capsaicin. However, in some cases the reactions seemed more severe than what was set out in the product labels. In other cases, which mostly concerned nurses who administered the treatments, the reactions, which at first were mild and manageable, became worse and lasted longer with repeated exposure. A few cases also described nurses who experienced adverse reactions even though they took the protective measures that were recommended in the labels and prescribing information, including wearing a mask, nitrile gloves and protective glasses.

Case examples

Here follow some cases that illustrate reactions that became worse and/or lasted longer with repeated exposure:

— A 42-year-old nurse had administered the Qutenza patch once or twice per week using nitrile gloves, mask, glasses and gown. At first, she had rhinitis and runny eyes which would disappear after 3 to 5 hours. A year later, she experienced dyspnoea and chest tightness which would disappear one hour after handling a patch. At the time of reporting, the nurse no longer administered patches.

— Three cases concerned nurses working at the same clinic and who treated patients with Qutenza. Over previous years there had been an increase in the number of treatments performed and the exposure to the substance had become more intense. The nurses had always felt the allergic symptoms, but they would disappear "up until a month ago" when they worsened and did not resolve. One of the nurses had never previously reacted to chili, but after eating chili-flavoured chocolate she reacted with a burning mouth and throat for 24 hours, as well as blisters in her mouth. She often had to use eye drops and lip balm to relieve dry and irritated eyes and lips. Occasionally, she also used over-the-counter analgesics. Another nurse, who started administering treatments in 2010, experienced irritated lips, eyes and mouth, as well as blisters in the mouth and a cough which would disappear initially. In 2016, her symptoms worsened and lasted longer, and as the symptoms in the eyes were present every day, she felt she had bad eyesight. It was also reported that previously the symptoms would disappear when off duty, but not anymore.

— A woman in her 60s had been treated four times with Qutenza with good effect. After each treatment with the patch, the patient's symptoms, including reduced taste, white tongue, coughing from throat irritation, and sore eyes, increased gradually. After the first two treatments she had so few side effects that she did not mention them at control visits. Following the fourth treatment, the symptoms "became a substantial problem". After the third, and especially the fourth, treatment she experienced adverse effects that persisted for four weeks. Symptoms were relieved by treatment with antihistamines.

Some other cases described reactions which seemed more severe than those set out in the product labels, especially for symptoms affecting the airways:

— A 52-year-old female HCP experienced irritated airways and severe persistent cough when applying a Qutenza patch. It was reported that her lung function was decreased, but initially improved with bronchodilators. Asthma was also reported, but treatment for that did not seem to improve her condition. Oral cortisone was also given, and the cough improved slowly but was triggered easily. The reporter described seriousness as a permanent disability.

— A nurse had received proper instructions on handling Qutenza for one patient. Upon opening the patch to treat a patient, she coughed severely and had to be treated with cortisone and anti-allergy medications, left the clinic/workplace and went home. The next day she returned to work and felt fine, but on entering the room where she had opened the patch, she started coughing severely again and had to be treated. At the time of reporting the nurse was recovering but still had a hoarse voice.

Another interesting case described a sales representative who experienced severe reactions just from being in the room where capsaicin was administered to a patient:

— A 58-year-old female sales representative experienced numbness and swelling of the tongue, cough, severe pruritis, and burning/irritation of the eyes during administration of the capsaicin patch to a patient. She was not in direct contact with the patch but was near it and did not wear any protection. She was treated with antihistamines and all events resolved on the same day except for numbness and swelling of the tongue, which resolved three days later. The swollen tongue event was described as a "very heavy reaction" according to the physician. It was reported that, ever since experiencing these reactions, the sales representative would wear protection and did not have any more problems.

Discussion and conclusion

Although many of the reactions reported in the case series are described in product labels and prescribing information, the severity of some reactions is not reflected there, and the reactions, even if starting out mild, could become more severe and even chronic with repeated exposure. Our case series also indicates that nurses and other HCPs administering Qutenza could be especially vulnerable to the increased severity of reactions, probably due to more frequent exposure. Although protective measures and other recommendations exist for HCPs, despite adhering to them individuals can still experience capsaicin-related symptoms, and as some of the cases demonstrated, the reactions may become worse and even chronic with repeated exposure. It would therefore be wise to review the risk minimization guidelines, and to consider including recommendations for HCPs to stop giving capsaicin treatments if they have reacted once before, to avoid further complications. In addition, it could also be prudent to consider protective equipment for anyone who is in a room where capsaicin is being administered, even if they themselves do not handle the product.

As mentioned, the labels do not seem to reflect the severity of some reactions, which are often described as mild. In our case series, this seems especially true for symptoms related to the airways. For example, the reaction 'cough' is labelled, which sounds mild, but in one case the cough was so severe that the affected nurse had to be treated with cortisone and anti-allergy medications. In another case, the nurse experienced a decreased lung function. In addition, 26 cases of dyspnoea were noted. Dyspnoea is not listed in capsaicin labels. However, for the cream formulation, it is described that there have been few reports of dyspnoea. Considering this, it could be worth also to clarify in the labels that it is possible to experience more severe reactions than those currently given.

References

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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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