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SGLT2 inhibitors and risk of toe amputation

Quick Read
Diabetic patients taking sodium/glucose cotransporter 2 (SGLT2) inhibitors may be at increased risk of toe amputation. Measures to minimize this risk should be borne in mind.

Canagliflozin, dapagliflozin and empagliflozin are sodium/glucose cotransporter 2 (SGLT2) inhibitor oral antidiabetic agents. They block renal protein SGLT2, which resorbs glucose from urine back into the bloodstream. Decreased removal of glucose from urine leads to a reduction in blood glucose levels. Medicines from this therapeutic class are indicated in adults with type 2 diabetes mellitus to improve glycaemic control in addition to diet and exercise. They are administered as monotherapy in patients for whom metformin is deemed inadequate on account of intolerance or contraindication. They can also be prescribed with other antidiabetic drugs including insulin, whenever these drugs do not achieve adequate control of blood glucose.

Two long-term, placebo-controlled clinical trials (**CANVAS and CANVAS-R**) have pointed to an increased risk of amputation, especially at first toe and metatarsal level, in patients on canagliflozin. The underlying mechanism is not known and has been the object of intense discussion. Assuming this can be a class effect, one theory suggests that the reduction in plasma volume associated with SGLT2 inhibitors may lead to decreased peripheral circulation, especially in patients in whom the latter is already compromised. By analogy, a study from as early as 2004 (Erkens JA et al) associated the use of diuretics with lower limb amputation. Such evidence has more recently been reinforced by a cohort study (Potier L et al).

In March 2017, following publication of the CANVAS/CANVAS-R studies, the potential risk of amputation with SGLT2 inhibitors was assessed by the PRAC (Pharmacovigilance Assessment Committee) at the European Medicines Agency (EMA). This assessment resulted in a recommendation that was at the time disseminated by Infarmed to include a warning in the Summary of the Product's Characteristics (SPC) and in the Information Leaflet. No increase in lower limb amputations has been seen with other medicines from the same class (dapagliflozin and empagliflozin). However, the

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above recommendation included these drugs as well in that, in the absence of data, it was considered that the same risk can apply to them on account of a possible class effect.

In fact, two cases have recently been reported in Portugal of toe amputation in diabetics on dapagliflozin, and a preliminary search in the European adverse drug reaction database (Eudravigilance) turned in a total of sixteen cases that could possibly be related to this risk.

Given all the above, the recommendations for **minimization of the risk of toe amputation in patients on dapagliflozin or other medicines of the same therapeutic class** are revisited here:

- Patients with risk factors for lower limb amputation, such as poor diabetic control, or at cardiovascular or vascular risk, should be closely followed.
- In patients who develop pre-amputation events, such as lower limb skin ulcers, infection, osteomyelitis or gangrene, treatment discontinuation should be considered.
- Good hydration and routine preventive foot care should be ensured, and patients should talk to their doctor in case of foot problems, such as wounds, discolouration or pain.
- Any suspected undesirable effect, namely amputation or pre-amputation event, that can be related to these medicines, should be reported on Portal RAM.

Adriana Gamboa

Farmacovigilância em Portugal: 25 anos ***E-book***
Chapter 7.6. – Neuropsychiatric Adverse Reactions (Mário Miguel Rosa)

Neuropsychiatric adverse reactions correspond to around 15% of all adverse drug reactions and can be found in every single Summary of the Product's Characteristics.

In pharmacovigilance identifying and classifying these reactions can be a problem. Unlike other similarly highly specialized organ systems, such as the hepatic, the nervous system does not present a monotonous response and hundreds of different signs and symptoms can be caused by drugs. On the other hand, some of the reported symptoms are highly prevalent in the general population (e.g., headache), which further complicates causality assessment.

This e-book chapter provides the reader with basic but systematic information on the peculiarities of the nervous system, the pathophysiology of the adverse reactions affecting it and the adverse reactions that are most commonly reported for each subgroup of neurological presentations.

To know more you can look up this chapter or download the whole *eBook* here

ADRs in the Literature
Non-intended impact of medicinal product safety information communication

In this recent Drug Safety article, the authors undertook a critical review of publications on non-intended (or unplanned) effects of communications to the public containing safety information on medicines. They studied **communications issued by regulatory bodies (e.g., FDA) and the media, as well as advertising aimed at consumers.** Of the **26 studies** reviewed, 23 were based on data from the USA, one from Canada, one from the United Kingdom, and one from the Netherlands.

The authors identified six main categories of non-intended post-safety information effects (Table below), of which the most common was **discontinuation or decreased use of the medicine** in question.

Category ***(no. of studies where it was identified)***
Discontinuation or decrease in use (21)
Substitution for a different medicine or therapy (6)
Spillover effects (5) into off-target populations, such as for example adults when the safety communication referred to paediatric patients only
Changes in knowledge, attitude or beliefs (4) – e.g., change in safety comprehension or risk perception as described by the patient or by the physician themselves
Change in diagnoses (4) – e.g., decreased incidence of records of clinical diagnosis of the condition for which the target medicine is indicated
Changes in clinical practice (4) – e.g., more diagnoses of depression in psychiatry and fewer in primary care following safety information on antidepressants
Other behavioural changes (4) – e.g., increased incidence of self-harm in patients taking an antidepressant regarding which a safety communication has been issued

One of the limitations of this review was its inability to establish a cause for the communication effects, since communications may have reached the public from various sources and with varying content, making it **difficult to determine the relative weight of each factor** for the observed outcome. In addition, and even though this is not alluded to in the article, the high proportion of studies based on US data may compromise their extrapolation to Europe or other regions.

Moreover, the actual intended effect is not clear for a number of communications. Since most studies were concerned with the effects of safety communications on the risk of antidepressant use, **extrapolation to other pharmacological classes is not straightforward**.

Inspite of the above limitations, the results of this review suggest that there is a potential for the occurrence of non-intended effects from the dissemination of safety information to the general public. This raises the issue of which can be the best way to communicate with patients. The authors suggest that defining **Safety Communication Best Practices** for prescription medicines should be a priority.

Sílvia Duarte

DeFrank JT, McCormack L, West S, Lefebvre C, Burrus O. Unintended effects of communicating about drug safety issues: a critical review of the literature. Drug Safety (2019) 42:1125–1134

Communications to Healthcare Professionals published on the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Irinotecan Onivyde lipossómico peguilado	At centres using Onivyde: **Physicians:** oncologists **Pharmacists:** hospital pharmaceutical services **Nurses:** day hospitals	Risck of medication error due to change in expression of strength and dose calculation 06-11-2019
Mitomycin Mitomicina-C Kyowa	**Physicians, pharmacists and nurses:** at oncology, urology, haematology and internal medicine departments, as well as hospital pharmaceutical services – of organizations still stocking affected batches before their expiry date	Administration of certain batches exclusively by intravesical route 20-11-2019

Compiled by Patrícia Catalão

Educational Materials published on the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Deferasirox Exjade – film coated tablets only	**Physicians:** imune-haemotherapy and haematology, paediatrics	Healthcare professional guide
	Patients	Patient guide 27-11-2019
Ethinylestradiol + Etonogestrel Ornibel	**Physicians:** gynaecologists, general/family physicians	Checklist for prescribing physicians
	Patients	Patient information card 06-11-2019
Pembrolizumab Keytruda	**Patients**	Information brochure Alert card 20-11-2019

Compiled by Patrícia Catalão

Portal **RAM**

Notificação de Reações Adversas a Medicamentos

Report an adverse drug reaction here.
Find answers to your questions about the ADR Portal here.