Newsletter
December 2018
Hydrochlorothiazide - Risk of non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)

The Egyptian Pharmaceutical Vigilance Center (EPVC) required the distribution of Dear Healthcare Professional Communication" (DHPC) from all Marketing authorization holders for Hydrochlorothiazide.

Pharmacoepidemiological studies have shown an increased risk of non-melanoma skin cancer (NMSC) (basal cell carcinoma, squamous cell carcinoma) with exposure to increasing cumulative doses of hydrochlorothiazide (HCTZ).

HCTZ containing medicinal products are widely used to treat hypertension, as well as cardiac, hepatic, and nephrogenic oedema or chronic heart insufficiency.

Two recent pharmaco-epidemiological studies conducted in Danish nationwide data sources (including Danish Cancer Registry and National Prescription Registry) have shown a cumulative dose-dependent association between HCTZ and NMSC (basal cell carcinoma, squamous cell carcinoma). Photosensitizing actions of HCTZ could act as possible mechanism for NMSC.

One study [1] included a population comprised of 71,533 cases of basal cell carcinoma (BCC) and 8,629 cases of squamous cell carcinoma (SCC) matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted odds ratio (OR) of 1.29 (95% confidence interval (CI): 1.23–1.35) for BCC and 3.98 (95% CI: 3.68–4.31) for SCC. A cumulative dose response relationship was observed for both BCC and SCC. For example, 50,000 mg cumulative dose corresponds to 12.5 mg HCTZ taken daily for about 11 years.

Another study [2] showed a possible association between lip-cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer (SCC) were matched with 63,067 population controls, using a risk-set sampling strategy.

NMSC is a rare event. Incidence rates highly depend on skin phenotypes and other factors leading to different baseline risks and varying incidence rates in different countries. Estimated incidence rates vary across different regions in Europe and are estimated at rates of around 1 to 34 cases per 100,000 inhabitants per year for SCC and 30 to 150 per 100,000 inhabitants per year for BCC.

Based on the results of the two Danish epidemiological studies, this risk might increase approx. 4 to 7.7-fold for SCC and 1.3-fold for BCC depending on the cumulative dose of HCTZ.

The Summary of Product Characteristics and Package Leaflet for all the concerned products will be updated to inform on the risk of NMSC associated with the use of HCTZ.

Recommendations:
- Patients taking HCTZ alone or in combination with other medications should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions as well as changes to existing ones and report any suspicious skin lesions.
- Suspicious skin lesions should be examined potentially including histological examinations of biopsies.
- Patients should be advised to limit exposure to sunlight and UV rays and use adequate protection when exposed to sunlight and UV rays to minimize the risk of skin cancer.
- The use of HCTZ may also need to be carefully reconsidered in patients who have had previous skin cancer.
Interaction between atorvastatin with the antivirals elbasvir/grazoprevir and glecaprevir/pibrentasvir, which showed increases in atorvastatin plasma levels with these co-administrations

Atorvastatin is a synthetic lipid-lowering agent indicated for the prevention of cardiovascular diseases as well as for the treatment of hypercholesterolaemia under certain conditions. Based on the review of the data on safety and efficacy, the benefit-risk balance of atorvastatin-containing medicinal products in the approved indication(s) remains unchanged. Nevertheless, the product information should be updated to include a warning on the effect of co-administration of atorvastatin with elbasvir/grazoprevir as well as the maximum dose recommended for atorvastatin in this situation. In addition, the product information should be updated to reflect a contraindication with glecaprevir/pibrentasvir, and to highlight the elimination pathway information for atorvastatin so that healthcare providers have all the information available as regards future interactions with atorvastatin-containing products.

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivatives, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, niacin, or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.
Case Report from Alexandria - Extravasation and Skin necrosis associated with the use of Dopamine & calcium gluconate in neonates

The regional center in Alexandria received a case report concerning a 2 weeks, 3.2 kgs, neonate admitted to the NICU since birth due to hypoxia where he was placed on mechanical ventilator. Dopamine (200 mg/5 ml) ampoule with dose of 5 microgram/kg/minute and 5.3 ml of calcium gluconate both were further diluted with 5 % glucose before their administration through neonate peripheral vein. After 4 days, he experienced administration site extravasation where the skin appeared white and on the next day skin necrosis occurred. Both dopamine and calcium gluconate solutions administration were hold once the extravasation occurred, Mebo and fucidin creams were applied to the damaged skin as a medical treatment for about 15 days. The neonate was recovering from the skin damage beside that he was examined by surgeon where he switched to babycare and vitro heal gel. Also, he recommended that the neonate should undergo plastic surgery as the skin necrosis is deep and will leave a scar.

Dopamine is a sympathomimetic amine, vasopressor, naturally occurring immediate precursor of norepinephrine. It acts on beta 1 receptors in cardiac muscle, and increases contractility with little effect on rate.

Calcium gluconate is the calcium salt of gluconic acid, an intravenous medication used to treat conditions arising from calcium deficiencies such as hypocalcemic tetany, hypocalcemia related to hypoparathyroidism, and hypocalcemia due to rapid growth or pregnancy.

Extravasation refers to the escape of a drug into the extravascular space, either by leakage from a vessel or by direct infiltration. Extravasation of a vesicant drug has the potential to cause tissue damage with severe and/or lasting injury.

Labeled information:
• According to dopamine 40 mg / ml concentrate for solution for infusion Summary of product Characteristics (SmPC) it was stated under section: (4.4 Special warnings and precautions for use): “Dopamine HCl should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue”.
• According to calcium gluconate injection Summary of product Characteristics (SmPC) it was stated under section: (4.8 Undesirable effects): “Calcinosis cutis, possibly followed by skin ablation and necrosis, due to extravasation, has been reported. Reddening of skin, burning sensation or pain during intravenous injection may indicate accidental perivascular injection, which may lead to tissue necrosis.

Recommendations for Healthcare Professionals:

Dopamine HCl:
• It should be infused into a large vein whenever possible.
• Higher concentrations of dopamine HCl should be infused through central venous catheter using a syringe pump to avoid extravasation and fluid overload.
• Ischemia due to dopamine HCl can be reversed by infiltration of the affected area with 10-15 ml of saline containing 5 to 10 mg phentolamine.
• A syringe with a fine hypodermic needle should be used to liberally infiltrate the ischemic area as soon as extravasation is not-
Dopamine HCl is incompatible with bicarbonate and other alkaline solutions.

**Calcium Gluconate:**

- Calcium salts are irritants. The infusion site must be monitored regularly to ensure extravasation injury has not occurred.\(^5\)
- Calcium gluconate should be injected through a small needle into a large vein in order to avoid too rapid increase in serum calcium and extravasation of calcium solution into the surrounding tissue with resultant necrosis.

**References:**

1. Drugs.com: “Dopamine SmPC” [Click here]
2. Rxlist.com: “Calcium gluconate SmPC” [Click here]
3. Uptodate.com: “Extravasation injury from chemotherapy and other non-antineoplastic vesicants” [Click here]
4. Emc.org: “Dopamine SmPC” [click here]
2. Emc.org: “Calcium gluconate SmPC” [Click here]
In the context of EPVC plan for pharmacovigilance awareness, a training and workshops were conducted for pharmacists the Natat Alexandria in cooperation with The National Liver Institute, Menoufia University.

Advanced Pharmacovigilance training for pharmacists at the National Liver Institute

In the context of EPVC plan for pharmacovigilance awareness, a training and workshops were conducted for pharmacists the Natat Alexandria in cooperation with The National Liver Institute, Menoufia University.
“Advances in PV Practice” training conducted at Faculty of Pharmacy – Menoufia University

In cooperation with Faculty of Pharmacy – Menoufia University, EPVC conducted pharmacovigilance training titled “Advances in PV practice.”
What is Pharmacovigilance

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

A call for reporting

Please remember that you can report safety information of medicines to EPVC using the following communication information:

Communications information

The Central Administration of Pharmaceutical Affairs
The Egyptian Pharmaceutical Vigilance Center

Address: 21 Abd El Aziz Al Soud Street. El-Manial, Cairo, Egypt, PO Box: 11451
Telephone: (+2)02 25354100/ (+2)02 23684288/ (+2)02 23648046/ (+2)02 23640368/ (+2)02 23648769
Extension: 1303
Fax: +202 – 23610497
Email: pv.center@eda.mohealth.gov.eg
Website: www.epvc.gov.eg
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