Dronedarone-induced hyperkalemia

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Summary

Hyperkalemia associated with dronedarone was identified as a potential signal in a screening of VigiBase, the WHO global database of individual case safety reports, at the Uppsala Monitoring Centre (UMC). As of April 2019, there were 18 unique cases from ten countries reporting hyperkalemia with dronedarone as a suspected or interacting medicine (expected eight). Dronedarone was the only product suspected in 12 cases. The average time from dronedarone start to the event onset (TTO) was 19 days (n=11), ranging from three days to nine weeks. Positive dechallenge was reported in six cases. In 11 cases, (acute) renal failure was a co-reported event, with creatinine increased in two other cases, while in five cases there were no co-reported renal events and in four
of these only dronedarone was suspected. Other drugs known to cause hyperkalemia were reported as suspected (four cases) or concomitant drugs (ten cases), such as beta-blockers and calcium channel blockers (which alter transmembrane potassium movement); ACE-inhibitors, angiotensin-II receptor blockers, NSAIDs, and potassium-sparing diuretics (which impair renal potassium excretion); and potassium-containing agents (which increase supply of potassium).

Based on the Bradford-Hill criteria, and especially the reporting disproportionality (observed 18 and expected eight), a close temporal relationship including positive dechallenge, and similar literature cases, a causal relationship for dronedarone and hyperkalemia seems possible.

The mechanism isunclear,butlikelytobemultifactorial:e.g.renal failure with dronedarone and concomitant medications known to cause
hyperkalemia as contributing factors. Health care professionals should be aware of this possible risk. Renal function should be monitored periodically as recommended during dronedarone treatment.

Introduction

Dronedarone is an anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds including amiodarone. Dronedarone (Multaq) is approved for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF) in the European Union (EU). Due to its safety profile (as highlighted in the sections of contraindication and warnings in the product information), dronedarone should only be prescribed after alternative treatment options have been considered. The recommended dose is 400 mg twice daily in adults.[1]

Hyperkalemia is a common clinical condition that can be defined as a serum potassium concentration exceeding 5.0 mmol/L. Hyperkalemia becomes a potentially life-threatening condition where serum potassium exceeds 5.5 mmol/l. It can be caused by reduced renal excretion, or excessive intake or leakage of potassium from the intracellular space. In addition to acute and chronic renal failure, hypoaldosteronism, and massive tissue breakdown (as in rhabdomyolysis), are typical conditions leading to hyperkalemia. Symptoms are non-specific and predominantly related to muscular or cardiac dysfunction.[2-4]

Drug-induced hyperkalemia is the most important cause of increased potassium levels in everyday clinical practice; it may be asymptomatic. However, it can be dramatic and life threatening, posing diagnostic and management problems. A wide range of drugs can cause hyperkalemia by a variety of mechanisms. Drugs can interfere with potassium homoeostasis either by altering transmembrane potassium movement or by impairing renal potassium excretion. Drugs may also increase potassium supply. The reduction in renal potassium excretion due to inhibition of the renin-angiotensin-aldosterone system represents the most important mechanism by which drugs are known to cause hyperkalemia[5].

- Medications that alter transmembrane potassium movement include amino acids, beta-blockers, calcium channel blockers, suxamethonium, and mannitol.

- Drugs that impair renal potassium excretion are mainly represented by ACE-inhibitors, angiotensin-II receptor blockers, direct renin inhibitors, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors (NSAIDs), heparin and derivatives, aldosterone antagonists, potassium-sparing diuretics, trimethoprim, and pentamidine.

- Potassium-containing agents represent another group of medications causing hyperkalemia.

The combination of dronedarone and hyperkalemia was detected in a screening of VigiBase, the WHO global database of individual case safety reports, at the Uppsala Monitoring Centre (UMC). The Bradford-Hill criteria were applied in the assessment of the case series to evaluate causality and possible risk factors for dronedarone associated hyperkalemia.

Reports in VigiBase

A clinical review of reports with hyperkalemia associated with dronedarone included in VigiBase up to April 2019 was performed; duplicates were excluded.

VigiBase contained 18 unique cases reporting hyperkalemia with dronedarone as a suspected or interacting medicine (expected eight). Dronedarone was the only suspected drug in 12 cases. The reports came from 10 countries (six from the USA, three from Sweden, two from the Republic of Korea, and one each from Austria, Germany, Italy, the Netherlands, Slovakia, Slovenia, and the United Kingdom). There were five females and 13 males, with an age range between 45 and 86 years (mean 71). The dronedarone dose was known in 11 cases: 400 mg once daily in two cases and twice daily in nine cases. A total of 89% (n=16) of the cases were serious, with four life-threatening and one fatal. When the information on potassium value was available, the maximum levels were reported as 5.4, 5.7, 6.0, 6.2, 7.1 and >7 mmol/L, respectively.

Where given (n=11), the average TTO was 19 days (SD=18) ranging from three to 63 days (not included TTO=6 years in a case reported by a non-physician with limited information, and TTO as “weeks” in one case). Positive dechallenge was reported in six cases when information was available. Based on the temporal relationship including positive dechallenge, there seems to be a possible causal relation for dronedarone associated hyperkalemia.

In 11 cases, (acute) renal failure was a co-reported event, with creatinine increased in two other cases, while in five there were no co-reported renal events and in four of these only dronedarone was suspected. While creatinine increased is clearly included in the label as an adverse reaction of dronedarone, renal failure is not.

Other drugs known to cause hyperkalemia were reported as suspected (four cases) or concomitant (10 cases): such as beta-blockers and calcium channel blockers (alter transmembrane potassium movement); ACE-inhibitors, angiotensin-II receptor blockers, NSAIDs, potassium-sparing diuretics (impair renal potassium excretion); and potassium-containing agents (increase potassium supply).

Literature and labelling

Hyperkalemia is not labeled in the product information.[1] Section 4.8 Undesirable effects mentions "Plasma creatinine increase ≥10% five days after treatment initiation" as very common.

In section 4.4 Special warnings and precautions for use the following is described: "Larger increases in creatinine after dronedarone initiation have been reported in the post-marketing setting. Some cases also reported increases in blood urea nitrogen possibly due to hypoperfusion secondary to developing CHF (pre-renal azotaemia). In such cases dronedarone should be stopped (see sections 4.3 and 4.4). It is recommended to monitor renal function periodically and to consider further investigations as needed."

Discussion

Dronedarone is a non-iodinated benzofuran developed specifically for the treatment of AF, designed to retain the efficacy of amiodarone, but with an improved safety profile.[6] However, due to its safety profile, dronedarone should only be prescribed after alternative treatment options have been considered.[1]

Based on 18 unique cases in VigiBase reported from 10 different countries, the close temporal relationship including cases with positive dechallenge seems to support a possible causal association between dronedarone use and hyperkalemia.

The etiology of hyperkalemia is often multifactorial, with impaired renal function, medication use, and hyperglycemia as the most common contributory factors.[7, 8]

The mechanism behind the possible causal relationship between dronedarone use and hyperkalemia is not clear. In 11 of the 18 cases, (acute) renal failure was a co-reported adverse event, with creatinine increased in two other cases. Therefore, renal impairment might have contributed to the occurrence of hyperkalemia following dronedarone treatment. Currently, renal failure is not specifically labeled in the EU Summary of Product Characteristics of dronedarone[1] (Multaq). However, "Blood creatinine increased" is a well-known adverse reaction with a frequency as "very common": "≥ 10% five days after treatment initiation". There are also detailed warnings on "Management of plasma creatinine increase". As post-marketing experiences, "increases in blood urea nitrogen possibly due to hypoperfusion secondary to developing congestive heart failure (pre-renal azotaemia)" is also mentioned.

Potassium is the most abundant intracellular cation (100 - 150 mmol/l) and is critical in many physiological functions. In healthy subjects[9], dronedarone reduces renal creatinine and N-methylnicotinamide (NMN) clearance by about 18%, without evidence of an effect on glomerular filtration rate, renal plasma flow or electrolyte exchanges. This suggests a specific partial inhibition of tubular organic cation transporters. A limited increase in serum creatinine is therefore expected with dronedarone treatment but does not mean there is a decline in renal function. It was stated that no clinically relevant changes were observed in the laboratory tests. No changes in urine fllow rate, osmolality, sodium and potassium excretions were observed between the baseline and day 7 of dronedarone treatment compared with placebo. However, no results have been presented on potassium levels.

Dronedarone and renal impairment has been evaluated in the Italian[10] as well as Spanish post-marketing reports, together with review of the literature.[11] Tarapués et al[11] showed that the reporting odds ratio was 2.88 (1.52-5.46). Positive dechallenge was observed in five of ten cases. In addition, eight cases of renal failure were found in the medical literature. It was concluded that the effect

of dronedarone on the renal function is supported by limited information; and based on cases from spontaneous reporting systems and those from the medical literature, there was a potential relationship between dronedarone use and renal impairment.

In 2012, Biagi et al[10] reported nine cases of renal impairment (mostly acute renal failure) among the Italian post-marketing reports of dronedarone. Interestingly, three cases of hyperkalemia were noted (blood potassium levels 5 mmol/l, 5.6, and 9.6 mEq/l, respectively). However, none of these 18 hyperkalemia cases in VigiBase were reported from Italy, indicating an under-estimation of the dronedarone-related hyperkalemia, either due to under-reporting, or due to incomplete coding of cases or searches in VigiBase.

In addition to renal impairment as a contributing factor, other medication use, and hyperglycemia may also play a role as risk factors. There were concomitant medications known to cause hyperkalemia such as beta-blockers and calcium channel blockers, ACE-inhibitors, angiotensin-II receptor blockers and potassium-sparing diuretics. Among the 18 cases, seven were taking medications for diabetes, although hyperglycemia was not specifically mentioned.

Conclusion

Based on the Bradford-Hill criteria, and especially the reporting disproportionality, close temporal relationship including positive dechallenge, and similar literature cases, a causal relationship for dronedarone and hyperkalemia seems possible. The mechanism is unclear, but likely to be multifactorial, e.g. renal failure with dronedarone and concomitant medications known to cause hyperkalemia as contributing factors. Health care professionals should be aware of this possible risk. Renal function should be monitored periodically as recommended during dronedarone treatment.

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 consideration in the same way as any scientific document. patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical 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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