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Evaluation of Hypokalemia Associated with Ondansetron in Pediatric Oncology Patients

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Abstract

Before administering chemotherapy, ondansetron, a 5-hydroxytryptamine (5-HT3, serotonin) receptor antagonist, is used as an antiemetic prophylactic. Ondansetron has a rare side effect called hypokalemia, which may go unreported because it is confused with emesis and chemotherapy-induced tubulopathy. We conducted a prospective cohort research to find out if renal potassium squandering caused by ondansetron resulted in severe hypokalemia independently. Ten of the twelve patients who were enrolled in the trial finished it. Prior to and during the administration of ondansetron, blood and urine samples were taken from patients who had been admitted for intravenous (IV) hydration and chemotherapy. To determine the salt and potassium balances, dietary histories and IV records were examined. The expected decrease in urine osmolality and rise in urine sodium were seen, but there was no statistically significant difference in the salt or potassium balance between the pre- and post-ondansetron periods. In individuals who are adequately hydrated and have a sufficient intake of nutrients, ondansetron does not significantly worsen potassium depletion. In patients receiving this drug who have on-going dietary or volume status deficiencies, careful monitoring of serum potassium levels is advised.

Keywords: Pediatric Oncology; Cancer; Education; Hydration and chemotherapy; Pediatric surgery; Pediatric pathology; Patient-reported outcomes

Introduction

In children with cancer, ondansetron, an antiemetic, is given in addition to chemotherapy. It is a highly effective selective 5-HT3 receptor antagonist with a great safety profile. The emergence of hypokalemia is a rarely mentioned adverse effect. Ondansetron itself, the impact of chemotherapy on renal tubular function, emesis-induced alkalosis, or a combination of variables may all contribute to hypokalemia. Ondansetron has the potential to cause hypokalemia through altering renal tubular physiology, according to in vitro research. In the nephron, ondansetron has two distinct effects. Ondansetron first inhibits the Na+-K+-2Cl-(NKCC2) transporter at the level of the Loop of Henle, increasing sodium supply to the distal nephron. Ondansetron then up regulates the Na+-K+ ATPase throughout the nephron, and in particular the distal tubule, this in turn needs K+ excretion via the ROMK potassium channel to promote the electro neutral reabsorption of sodium via the epithelial sodium channel (ENaC) from the distal nephron. By reducing intracellular sodium levels in distal tubular cells that express ENaC and so boosting tubular sodium entry at this segment, this worsens renal K wasting. In order to preserve electrical neutrality, this ultimately calls for greater K secretion into the urine via ROMK. Based on in vitro findings, ondansetron appears to have a unique effect on the renal tubules that is not shared by other selective 5-HT3 antagonists [1].

Ondansetron was identified as a likely culprit after analysis of a previous report that linked the drug's use to the repeatable onset of hypokalemia in a child with cancer. The patient's transtubular potassium gradient (TTKG) and potassium level both restored to normal levels after 24 hours of stopping ondansetron. One month later, the patient was readmitted for IV cyclophosphamide therapy, and ondansetron was given as usual as antiemetic prophylaxis. Given the patient's volume status, the TTKG increased excessively high, and the patient's plasma potassium level decreased at the same time [2].

We questioned in that case report whether ondansetron-related hypokalemia was a lesser known phenomenon because of the confounding factors of chemotherapy toxicity and vomiting-induced changes in K. In order to find out (1) whether renal potassium wasting occurs frequently in paediatric oncology patients receiving ondansetron and (2), if it does, which factors increase the likelihood of potassium wasting in paediatric oncology patients, particularly in those developing clinically apparent hypokalemia, we conducted a prospective study of patients receiving chemotherapy with ondansetron [3].

Materials and Methods

We created a prospective cohort research based on the previously published case report to see if hypokalemia related to ondansetron use was an unrecognised side effect. The study protocol was approved by the Biomedical Panel of the Health Research Ethics Board at the University of Alberta in Canada. From January 2008 to August 2008, participants were progressively enrolled and gave their consent in the trial at the Stollery Children's Hospital in Edmonton, Alberta's outpatient paediatric oncology clinic. Patients who needed chemotherapy administration and where planned prophylactic ondansetron treatment was anticipated were chosen to participate. Therefore, intravenous cyclophosphamide, cisplatin, ifosfamide, and/or high-dose methotrexate therapy were the only available chemotherapy regimens.

All patients enrolled in the research underwent hydration prior to the administration of ondansetron and chemotherapy to exclude any potential effects of high aldosterone levels associated with intravascular

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volume depletion and consequent enhancement of renal potassium wasting. Patients who were unable to voluntarily provide a urine sample, who at the time of study entry had protracted vomiting that was resistant to anti-emetic therapy, who had taken ondansetron within 48 hours of enrolling in the study, or who were taking potassium supplements for any reason were all excluded from the study. On joining the study, there were no patients with primary renal or adrenal malignancies, kidney involvement from known cancers, or history of diuretic usage [4].

At the time of admission, information about the patient's age, gender, height, weight, diagnosis, and chemotherapy regimen was gathered. A food history and IV fluid record were gathered, and sodium and potassium intake and output were computed for each patient throughout the pre- and post-therapy study period in order to evaluate sodium and potassium balance. Serum samples were taken to measure plasma osmolality, potassium, and sodium, aldosterone, and creatinine levels before the ondansetron dose was administered. Before ondansetron delivery and a few hours after serum samples, urine samples were collected. For urinalysis, osmolality, potassium, sodium, and creatinine measurements, urine was taken. As well as 1 to 8 hours before and at least 8 hours after ondansetron dosing, urine volume was assessed. Prior to the injection of high-dose methotrexate, cyclophosphamide, if sphamide, or cisplatin, IV hydration was given to ensure euvolemia was reached. Prior to chemotherapy administration, patients who displayed signs of intravascular volume depletion were given additional boluses of intravenous normal saline to make up for their volume deficit, at the attending oncologist's discretion. During the course of the trial, ondansetron was administered to each patient at least once, either orally or parenteral in accordance with the product monograph provided by the manufacturer [5].

Discussion

To ascertain whether renal potassium wasting is a frequent occurrence associated with ondansetron treatment, we carried out a prospective cohort analysis of chemotherapy patients. We have shown that ondansetron does not seem to be related with increased renal potassium output when intravascular volume contraction and pre-existing tubulopathy leading to hypokalemia are accounted for. The majority of the time, two factors affects how potassium is handled by the kidneys. The amount of potassium in the renal tubule is firstly affected by renal tubular flow; the faster the flow, the more likely it is that the potassium concentration in the tubule would be diluted. By maintaining high gradients that encourage potassium secretion into the lumen, keeping low tubular potassium content makes it easier for potassium to be secreted. Dehydration or the use of angiotensin-converting enzyme inhibitors can cause low tubular flow conditions, which can impair potassium secretion and cause hyperkalemia. Second, to enable tubular potassium secretion, the renal tubule must create both chemical and electrical gradients in the distal nephron. As previously mentioned, the amount of sodium delivered to the distal nephron and the presence of aldosterone, which facilitates both apical sodium entry into the cell and potassium efflux from the cell into the urine, are important factors affecting the amplitude of the gradient [6].

In order to reduce the impact of aldosterone on the measurement of potassium in the urine, our experimental design purposefully took use of a hydration phase of medication. We see that aldosterone levels remained stable throughout the investigation. First, because of the small sample size, we included Patient 9, who actually saw an increase in aldosterone throughout the research, which is why we think this is the case. After looking through the data, we were unable to see any proof of volume loss due to gastrointestinal, gastrointestinal bleeding, or other causes to account for the physiologic rise in aldosterone. In addition, there was no proof that the main illness affected adrenal function, which would have been necessary to explain autonomous mineralocorticoid synthesis. The fact that our lab is unable to report plasma aldosterone levels below 69 pmol/L is the second explanation for the observed no statistical variance in aldosterone levels. Any value reported as "69" was assessed as 69 pmol/L for the analysis's purposes. However, changes in the volume status that was clinically relevant happened throughout the observation period, which was confirmed by the considerable decrease in urine osmolality. Urine osmolality gives an indirect measurement that implies antidiuretic hormone (ADH) activity was eliminated after the hydration phase, despite the fact that antidiuretic hormone (ADH) was not assessed. This led to the discovery that in half of the study subjects, the major outcome measure of TTKG could not be used [7].

In order to find out if renal potassium wasting is a frequent occurrence linked to ondansetron treatment, we performed a prospective cohort analysis of patients receiving chemotherapy. Ondansetron does not seem to be linked to excessive renal potassium release, at least not when intravascular volume contraction and pre-existing tubulopathy leading to hypokalemia are taken into account. Two variables primarily affect how potassium is handled by the kidneys. First, the amount of potassium in the renal tubule depends on renal tubular flow; the faster the flow, the more likely it is that the tubule's potassium content will be diluted. Because strong gradients favouring secretion into the lumen are maintained when tubular potassium content is kept low, potassium secretion is facilitated. Dehydration or the use of angiotensin-converting enzyme inhibitors can cause low tubular flow conditions, which can impair potassium secretion and cause hyperkalemia. Second, to enable tubular potassium secretion, the renal tubule must create both chemical and electrical gradients in the distal nephron. As previously mentioned, the amount of sodium delivered to the distal nephron and the presence of aldosterone-which promotes both apical sodium entries into the cell and potassium efflux from the cell into the urine-are important factors affecting the gradient's amplitude [8].

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Conclusion

Our research was designed to show whether ondansetron has a long-lasting relationship with renal K wasting. We acknowledge that our study has some drawbacks. First off, the sample size and duration of our study are both small. Because there are so many confusing drugs used in oncology therapy, it is impossible to say if a particular drug combination taken with ondansetron will cause K wasting in the urine. In a similar vein, even though none of our patients had pre-existing tubular dysfunction, we were unable to ascertain whether such dysfunction is necessary in order to cause K wasting when ondansetron is administered. Our group, which is rather diverse, does, however, show that clinically significant hypokalemia was not linked with ondansetron use within the context of paediatric cancer therapy. Second, we designed our study with the purpose of adopting strict statistical guidelines. For example, we calculated the sample size using a power of 90%, which is stricter than usual. In order to account for patient dropout or the potential for missing data, we recruited 12 patients even though the sample size was intended to be 7 individuals. According to our observations, only five patients were able to get their TTKGs analysed. Despite the fact that this shows that the trial is underpowered based on the primary outcome, we acknowledge that if a standard power of 80% had been utilised, we would have needed fewer patients-only 5 in total. We do, however, note the limited sample size and the potential for failing to identify a substantial difference in a negative study, which are both limitations.

We continue to believe that ondansetron does not seem to be linked to clinically important hypokalemia. Although one patient had clinically obvious hypokalemia, our cohort did not show a negative potassium balance or the emergence of clinically significant hypokalemia when these factors were taken into account, together with adequate hydration, food intake, and potassium supplementation. Early on in the course of treatment, especially in patients with poor hydration status or poor nutritional status, care should be taken to ensure that maintenance potassium replacement is administered during ondansetron administration for chemotherapy-induced nausea prophylaxis.

Conflict of Interest

None

Acknowledgement

None

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