Carboplatin Area Under the Curve dosing in pediatric patients: influence of glomerular filtration rate measurement

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SUMMARY

Introduction: Carboplatin dosage methods are often based on renal clearance. An accurate determination of the glomerular filtration rate (GFR) can be obtained by measuring 51Cr-EDTA clearance; however, this method is laborious. For that matter, various formulae have been developed to estimate the GFR. The aim of this study is to compare carboplatin doses calculated by Mann/Pein formula with GFR measured by 51Cr-EDTA clearance and GFR estimated with Schwartz formulae in children.

Methods: All cancer paediatric patients whose GFR was measured by 51Cr-EDTA were included. GFR was also estimated with Schwartz formulae. To calculate carboplatin dose, Mann/Pein formula was used. A target Area Under the Curve (AUC) of 5 mg/ml/min was chosen. Carboplatin doses were calculated with two different values of GFR calculated previously.

Results: A total of 33 patients were identified with a median age of 10 years old (range 1-17), 63.6% were males. The median weight, height and BSA were 28 kg (range 8-84.4 kg), 137 cm (range 64-182 cm) and 1.04 m^2 (range 0,37-2,1 m^2) respectively. The mean of carboplatin doses calculated with GFR measured by 51Cr-EDTA was 274.3±135.7 mg and with GFR estimated with Schwartz formulae was 364.9±156.6 mg. The mean difference between methods was 90.6 mg, P<0.001.

Conclusion: Carboplatin doses calculated with GFR estimated by Schwartz were statistically higher than those measured with 51Cr-EDTA. This variability may be a risk factor leading to inadequate dosage of patients treated with carboplatin.

Key words: **Area under the curve, carboplatin, glomerular filtration rate.**

Dosificación de carboplatino por el Área Bajo la Curva en pediatría: influencia de la medida de la tasa de filtrado glomerular

RESUMEN

Introducción: Existen métodos de dosificación de carboplatino que emplean el aclaramiento renal. La tasa de filtrado glomerular (TFG) puede ser determinada de forma precisa mediante el aclaramiento de Cr51-EDTA, sin embargo, este método es laborioso. Por ello, diversas fórmulas se han desarrollado para estimar la TFG. El objetivo de este estudio es comparar las dosis de carboplatino calculadas empleando la TFG medida con Cr51-EDTA y la estimada con la fórmula de Schwartz en pediatría.

Métodos: Todos los pacientes oncológicos pediátricos a los cuales se les midió la TFG mediante Cr51-EDTA fueron incluidos. Las TFG fueron también estimadas con la fórmula de Schwartz. Para calcular la dosis de carboplatino se empleó la fórmula de Mann/Pein. Se seleccionó un objetivo de Área Bajo la Curva (AUC) de 5 mg/ml/min. Las dosis de carboplatino fueron calculadas empleando los dos valores de TFG obtenidos previamente.

Resultados: Se identificaron un total de 33 pacientes con una mediana de edad de 10 años (rango 1-17 años), el 63,6% eran hombres. La mediana de dosis de carboplatino calculadas con la TFG medida con Cr51-EDTA y la estimada con la fórmula de Schwartz fueron respectivamente 274,3±135,7 mg y 364,9 ±156,6 mg. La diferencia media entre métodos fue de 90,6 mg (p<0,001).

Conclusión: Las dosis de carboplatino calculadas con la TFG estimada por la fórmula de Schwartz fueron significativamente superiores a las obtenidas con la TFG medida con Cr51-EDTA. Esta variabilidad puede ser un factor de riesgo pudiendo provocar una dosificación inadecuada en pacientes tratados con carboplatino.

Palabras clave: **Área bajo la curva, carboplatino, tasa de filtrado glomerular.**

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INTRODUCTION

Carboplatin is widely used in pediatric oncology to treat different tumors. It is eliminated almost entirely by glomerular filtration, but even in patients with normal renal function, the systemic clearance rate varies greatly[1].

In children, carboplatin dosing based on renal function has been shown to result in more reproducible and reliable drug exposures than dosing based on surface area[2]. This method not only minimizes the risk of underdosing, and therefore reduces the risk of undertreatment, but also reduces the risk of overdose, which may be related to the risk of increased toxicity.

Since the administration of carboplatin based on renal function is now routine in clinical practice in many multicentre protocols, it is crucial to accurately assess renal function of children.

An accurate determination of the glomerular filtration rate (GFR) could be obtained by measuring radioisotope tracers clearance (such as 51Cr-EDTA). However, this method is laborious and difficult, particularly in children[3-4]. For this reason, various formulas have been developed to estimate the GFR. The most widely used formula in pediatrics is Schwartz's.

Since carboplatin administration represents the main actual result of estimating GFR in pediatric oncology, it seems wise to consider the potential impact of changing the methodology for estimating GFR on carboplatin doses in children with cancer.

The aim of this study is to compare carboplatin doses calculated by Mann/Pein formula with GFR measured by 51Cr-EDTA clearance and GFR estimated with Schwartz formulae in children.

MATERIALS AND METHODS

A retrospective observational study of all cancer pediatric patients whose GFR were measured by 51Cr-EDTA from June 2013 until July 2019 in our centre was conducted.

GFR was measured by 51Cr-EDTA and estimated with Schwartz formulae on all patients.

Demographics data, diagnosis and creatinine serum levels of patients included were collected.

To calculate carboplatin dose modified Mann/Pein formula was used:

Dose (mg/m^2) = target Area Under the Curve (AUC) × [raw GFR (ml/min) + 15 x Body Surface Area (BSA) (m^2)]

Theoric carboplatin doses were calculated regardless if the patient treatment protocol actually included this drug. Carboplatin doses were calculated with the two different values of GFR previously calculated. A target AUC of 5 mg/ml/min was chosen.

A descriptive analysis of outcomes was carried out. For quantitative variables, median and range were calculated as measures of central tendency and dispersion. For qualitative variables, measures of absolute, relative frequency and percentages were calculated. Student's t-test for paired samples was applied to compare mean estimated and measured GFR and carboplatin mean doses. A P value under 0.05 was considered statistically significant. Analyses were performed using the statistical package IBM SPSS Statistics 24®.

RESULTS

A total of 33 patients were identified with a median age of 10 years old (range 1-17) a 63.6% were males. The median weight, height, and body surface area (BSA) were 28 kg (range 8-84.4 kg), 137 cm (range 64-182 cm) and 1.04 m^2 (range 0.3-2.1 m^2) respectively.

Patients diagnosis were neuroblastoma 18.2% (n=6), osteosarcoma 12.1% (n=4), Ewing's sarcoma 12.1% (n=4), medulloblastoma 9.1% (n=3), non-Hodgkin Lymphoma 9.1% (n=3), hepatoblastoma 6.1% (n=2), rhabdomyosarcoma 6.1% (n=2) and others 27.2% (n=9).

The mean raw GFR measured by 51Cr-EDTA was 52.9±25.5 ml/min and the estimated with Schwartz formulae was 69.8±30.9 ml/min. The mean difference between the two methods was 16.9 ml/min (P<0.001)

The median carboplatin doses calculated with GFR measured by 51Cr-EDTA was 274.3±135.7 mg and the calculated with GFR estimated with Schwartz formulae was 364.9±156.6 mg. The mean difference between the two dosing methods was 90.6 mg (P<0.001).

Patients who would have been dosed by estimating GFR with Schwartz formulae would have received a mean 24.8% increased dose than if they were dosed by measuring GFR by 51Cr-EDTA.

DISCUSSION

Accurate determination of kidney function is difficult in children. Due to ethical and practical reasons, it is difficult for pediatric patients to measure GFR markers such as inulin, iohexol, 51Cr-EDTA or 99mTc-DTPA[5-6]. Several equations have been developed for pediatric patients[7-11]. The Schwartz formula, the most extensively validated formula, is based on serum creatinine, appear to overestimate GFR in children with decreasing kidney function when compared with measured inulin clearance. It should be noted that serum creatinine is affected by muscle mass, gender, diet, and renal tubular secretions. In children, serum creatinine may also be affected by diseases such as neuromuscular disease and anorexia nervosa[12].

With the purpose of evaluating the effect of GFR measurement for carboplatin dosing, we compared doses of carboplatin calculated with Mann/Pein formula using two different measures of GFR: one calculated measuring 51Cr-EDTA clearance and the other estimated with Schwartz´s formula. We found a statistically difference between the two methods, being carboplatin doses calculated by Schwartz formula considerably higher than those calculated with 51Cr-EDTA (90.6 mg, P<0.001).

Whether the magnitude of changes in carboplatin doses will affect the final clinical results has not been prospectively evaluated. The case heterogeneity of our study population (from which GFR study data is obtained) will make this analysis difficult. Most clinicians would consider a 10% dose change for any chemotherapeutic drug as being significant, in our study we identified a mean difference of 24.8% between methods.

Würthweina *et al.* 2011[13] compared different formulas employed to measure BSA, GFR and carboplatin dosing. They concluded that it is the choice of the GFR formula rather than the BSA equation or the carboplatin dose formula that determines the differences in carboplatin dosing, which remarks the importance of accurately measuring GFR. They also found marked differences in GFR when using different formulas and according to age groups; for Schwartz formula the estimated values of the GFR in young children were lower than the mean over all formulas evaluated and higher in the group of 16-year-olds. Skinner *et al.*[14] reviewed

the GFR values of 39 patients, including children, and found that the GFR measured in each patient differed greatly from the GFR estimated by Schwartz. In light of this, the estimation of GFR by measuring radioisotope tracers (such as 51Cr-EDTA) should be mandatory in pediatrics, especially with nephrotoxic drugs that can be administered accurately based on renal function, such as carboplatin.

In a given patient, only a correct carboplatin dose can achieve the desired target AUC. The nuclear medicine-based GFR estimation method and the adaptive dose formula currently used in our study have produced such completely different results. This degree of variation in GFR values may cause pediatric cancer patients to be at risk of severe toxicity or undertreatment of their cancer.

CONCLUSION

Carboplatin doses calculated with GFR estimated by Schwartz were statistically higher than those measured with 51Cr-EDTA. This variability may be a risk factor leading to inadequate dosage of patients treated with carboplatin.

GFR measured with 51-Cr-EDTA is considered the gold standard. Therefore, it should be implemented in all centres where carboplatin is dosed in pediatric patients.

Conflict of interests: The authors declare that they do not present a conflict of interest.

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