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Original Research

Carboplatin therapeutic monitoring in preterm and full-term neonates ☆

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Abstract ***Introduction:*** Administration of the most appropriate dose of chemotherapy to neonates is particularly challenging and frequently not standardised based on any scientific rationale. We report the clinical utility of carboplatin therapeutic drug monitoring in preterm and full-term neonates within the first month of life.

Methods: Carboplatin therapeutic monitoring was performed to achieve target drug exposures area under the plasma concentration–time curve (AUC values) in nine preterm and full-term neonates diagnosed with retinoblastoma or neuroblastoma treated over an 8 year period. Carboplatin was administered over 3 days with therapeutic drug monitoring utilised to target cumulative AUC values of 5.2–7.8 mg/ml min.

Results: AUC values achieved were within 15% of target values for the individual courses of treatment in all but one patient (12/13 courses of treatment), with dose modifications of up to 215% required to achieve target AUC values, based on initial mg/kg dosing schedules. Carboplatin clearance determined across three consecutive chemotherapy courses in two patients increased from 3.4 to 7.1 ml/min and from 7.2 to 16.5 ml/min, representing increases

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of 210–230% over several weeks of treatment. Complete remission was observed in 8/9 patients, with no renal toxicity reported and only one patient experiencing ototoxicity.
Conclusion: The study highlights the benefits of utilising therapeutic drug monitoring to achieve target carboplatin AUC values in preterm and full-term neonates treated within the first few weeks of life, particularly in view of marked increases in drug clearance observed over consecutive chemotherapy courses. In the absence of therapeutic drug monitoring, body-weight based dosing is recommended, with dosing guidance provided for both approaches to inform future treatment.

1. Introduction

The treatment of cancer in very young children represents a major clinical challenge. Developmental physiological changes within the first few weeks of birth have the potential to markedly impact drug disposition, making selection of the most appropriate dosing regimen particularly difficult [1–4]. While dose reductions are commonplace for the vast majority of anticancer drugs utilised in infants and very young children, with reduced dosing regimens commonly defined as being applicable below a specific age or body weight, these dose reductions are largely defined for children between 3 and 12 months of age [5]. The treatment of preterm and full-term neonates in the first few weeks of life needs to be approached judiciously, with the aim of achieving meaningful drug levels to exhibit anti-tumour efficacy, but without adversely affecting the developing child.

A key challenge in this area is the limited amount of data available concerning anticancer drug disposition in the neonatal patient population. However, for those drugs where studies have been reported, clearance values have frequently been shown to differ markedly from those seen in older children and adults [6]. Indeed, this is not surprising when we consider the continuing development and maturation of renal and hepatic function within the first few weeks of life, which may significantly impact on drug metabolism and elimination [7,8]. The generation of an increased volume of drug disposition data in this patient population is essential if we are to positively impact on the treatment of preterm and full-term neonates with cancer through the provision of meaningful dosing regimens based on 'real world' data.

The platinum agent carboplatin represents one of relatively few anticancer drugs where information gathered from clinical pharmacology studies has directly impacted on its clinical use in children with cancer. As removal of carboplatin from the body occurs almost exclusively via elimination of unchanged drug in the urine, initial doses are commonly based on renal function as defined by the glomerular filtration rate (GFR) of the patient [9,10]. In addition, exposure to carboplatin is commonly targeted to a defined area under the plasma concentration–time curve (AUC), which has been shown to more closely correlate with clinical parameters including toxicity and response than the dose administered [11,12].

Based on our current knowledge of the pharmacology of carboplatin, changes in kidney function are highly likely to impact on drug disposition. At birth renal function is anatomically and functionally immature, with marked increases during the first 2 weeks of life due to changes in renal vascular resistance and active nephrogenesis occurring between 9 and 36 weeks from birth, with accompanying changes in renal blood flow [13,14]. GFR values of 2–4 ml/min/1.73 m^2 are commonly observed in full-term neonates, with values as low as 0.6–0.8 ml/min/1.73 m^2 in preterm neonates [14,15]. While the kidney of the newborn is sufficient for normal growth and development, it provides limited adjustment to a stressful catabolic state which may be observed in sick preterm infants [16]. These changes with advancing gestational and postnatal age provide real potential for differences in drug clearance to be observed in neonates as compared to older children. In this respect we previously published a case report of a preterm infant treated with carboplatin, highlighting the potential for marked changes in drug clearance with age and requirement for increasing doses of carboplatin to achieve defined target AUC values [17].

In the current study we report on the wider clinical utility of carboplatin therapeutic drug monitoring in nine preterm and full-term neonates being treated for retinoblastoma and low risk neuroblastoma within the first weeks of life. Publication of these data in a small but significant patient population allow us to provide clear guidance for clinicians which will positively impact on the future treatment of preterm and full-term neonates with carboplatin. This is clearly an important issue considering a recent report that younger children are at an increased risk of experiencing ototoxicity following treatment with carboplatin [18].

2. Patients and methods

2.1. Patient treatment

Nine preterm and full-term neonates, studied over an 8 year period, received carboplatin treatment at six clinical centres as part of their standard treatment. Patients

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