Mini Review

Journal of Neonatal Studies

Antibiotics: Responding to a Global Challenge

Abstract

The miracle of antibiotics is hard to exaggerate. Each day, in every corner of the world, antibiotics improve, or could be improving outcomes in the septic neonate, the child with pneumonia, the new mother after a complicated delivery, the patient undergoing surgery, the nursing home resident with a urinary tract infection, the patient being treated of cancer, or the trauma patient on life support. The miracle also keeps our animals healthy for effective food production. But the miracle of these 'wonder drugs' is under threat and may be short lived: antimicrobial resistance is relentlessly increasing, especially for Gram negative organisms, prompting the oft expressed concern that we are plummeting headlong back into the pre-antibiotics era where clinicians and families once again will have to stand by and watch patients and loved ones die from once easily treated infections. Better diagnostics, especially those that are useful at the point of care to guide clinical decision making about whether and what agent to prescribe. These diagnostic tests should be affordable and feasible also in resource-poor settings.

Keywords: Strain consortiums • Pharmaceutical small pollutants • Consortiums

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Introduction

Enhanced understanding of how antibiotics are processed in the body, their effect on an individual's microbiological ecology, and studies of treatment efficacy and effectiveness. Enhanced surveillance on the incidence of infections, the way they are currently treated, clinical outcomes, and the influence of antimicrobial resistance, so we can better know where we are headed and model the effect of any possible changes in practice. Data will need to be clinically useful and better used in informing clinical decision-making, clinical guidelines and policy development. Associated costs and cost effectiveness. Improved ways of achieving translating new, robust evidence in clinical care in a wide range of settings internationally improving prevention of infections through changed lifestyle of individuals and communities, better farming methods, improved immunization and reduced opportunities for transmission [1]. Enhanced access to effective antibiotics for those who will benefit and better ways of curtailing use where they are not effective How different classes of antibiotics, infection related strategies, and antibiotic use in humans and animals interact to produce both beneficial and unwanted outcomes. We need to see the world in an integrated, systemic way. The bibliographic search was performed electronically using PubMed, as the search engine, until February 2nd, 2010. Medline search terms were as follows: pharmacokinetics AND (penicillin OR cephalosporin OR aminoglycosides) AND infant, newborn, limiting to humans. Penicillin, cephalosporin and aminoglycosides are fairly water soluble and are mainly eliminated by the kidneys [2]. The maturation of the kidneys governs the pharmacokinetics of penicillin, cephalosporin and aminoglycosides in the neonate. The renal excretory function is reduced in preterm compared to term infants and Cl of these drugs is reduced in premature infants. Gestational and postnatal ages are important factors in the maturation of the neonate and, as these ages precede, Cl of penicillin, cephalosporin and aminoglycosides increases. Cl

and t1/2 are influenced by development and this must be taken into consideration when planning a dosage regimen with these drugs [3]. More pharmacokinetic studies are required to ensure that the dose recommended for the treatment of sepsis in the neonate is evidence based. Intravascular arterial access is used during neonatal intensive care for continuous accurate monitoring of arterial blood pressure, to measure arterial blood gases and to provide a reliable source of blood sampling. Commonly used arterial access sites are the Umbilical Artery Catheter (UAC) and catheterization of some peripheral arteries, such as the radial artery. When neither the umbilical nor peripheral arteries are available, it is possible to establish arterial access using a Femoral Arterial Catheter (FAC). This route is commonly used in adult and pediatric intensive care, but is less commonly used in neonatal care, where it is seen as a 'last resort' for establishing arterial access. A survey of practice across UK regional neonatal intensive care units in 2014 found that they were in use in 16 of 40 (41%) units. Guidelines published online from several neonatal units in various countries also refer to the use of FACs in neonatal intensive care [4]. The leg has some protection against ischemic injury during FAC insertion from collateral arteries, but limb ischemia remains an associated risk with potentially life long implications. Concern about limb ischemia was the most commonly reported reason why units did not use FAC in a previous survey. There may also be concerns that the proximity of the FAC insertion site to the nappy of the area of the baby may also increase the risk of catheter related infection.

Results

Immaturity of humeral, cellular and myeloid cell line immunity places the neonate at higher risk for infection than older infants and children. The physiological conditions of neonates are different from those of adults. Neonates have a larger extracellular fluid volume they also have immature liver and kidney functions as well as higher plasma concentrations of bilirubin and non-esterified fatty acids. The water content is larger in preterm than in term infants and penicillin, cephalosporin and aminoglycosides are fairly water soluble and are distributed in larger volume in preterm than term infants. These antibiotics are mainly eliminated by the kidneys and their renal glomerular filtration and tubular secretion are reduced in the neonate. The reduced renal excretory function affects the disposition of penicillin, cephalosporin and aminoglycosides and their Clearance (Cl) is reduced in newborn infants compared to children [5]. The Volume of Distribution (V_d) of penicillin, cephalosporin and aminoglycosides tends to be larger in the neonate than in the adult because of the larger water body content in the neonate. It was difficult to be precise about the rate of infection due to FAC. By a conventional definition, the rate of CABSI was between 5.3 and 9.6/1000 days of care. All of these babies also had CVL in place, so it is not possible to know how many, if any, of these infections were due to the FAC. The calculated rate appears to be within the reported rates of CABSI reported in other neonatal populations [6].

In our series, 15% (15/97) of babies with a weight above 1000 g had a failed procedure, with removal of the catheter shortly after insertion due to impaired limb perfusion, but the rate of ischemic injury in this group was only 2% (2/97). Overall, outcomes were good in babies with a weight above 1000 g at the time of insertion, with no pre-existing evidence of lower limb arterial vulnerability, and who had catheters removed as soon as impaired perfusion was recognized. Ischemic injuries did occur in our cohort and there is clearly a risk of causing injury with FAC insertion. The overall rate of ischemic injury in our cohort was 4%. In 4 of the 6 babies who sustained an injury in our cohort, the weight at insertion was below 1000 g. There were also other pre-existing reasons to suspect that limb perfusion could be compromised by FAC insertion that were not appreciated prior to the insertion in 4 of these 6 babies. In 5 of the 6 babies with ischemic injury, there was a delay between the recognition of the poor limb perfusion and FAC removal [7]. Our data do not show that the duration of delay between the recognition of the ischemia and the removal of the FAC is greater in the babies who subsequently experienced ischemic injury compared to the duration of delay in those who did not experience an injury, but the number of injuries in the cohort is low, so this could be a type 1 error. This experience is based on observations at a single centre and we have no information about the rates of complication seen in other centers, so generalizability of these results is not assured. The decision to site any arterial catheter in a baby undergoing intensive care should always be made after careful consideration of the likely risks and benefits for that individual patient. In many babies adequate

monitoring can be provided using less invasive techniques for monitoring (for example; non-invasive blood pressure monitoring, functional echocardiography, pulse oximetry, end tidal capnography, capillary blood gas measurement). Given the margin of error associated with each of these techniques however, it may be beneficial to use an arterial catheter for monitoring in the sickest babies, with the highest requirement of respiratory or circulatory support [8].

Discussion

Such a cell cycle delay can function as a checkpoint to protect the cell's genetic integrity. Since there was no change in cell number at this time point, it was imperative to check if this effect persisted when the UV treated cells were allowed to grow and divide further. The cell number at 72 h post UVR in the White and Black skin melanocytes showed an insignificant decrease, whereas Hispanic skin melanocytes showed significant response (cell number was same as T0, but less than T Con) to UVR-induced modulation of growth. Overall, at 72 h post UVR, there was a reduction in expression of Ki67 and CyD1 in all three types of melanocytes but this reduction was significant in Hispanic skin melanocytes indicating that in spite of similar constitutive levels of melanin, susceptibility to UVR of White and Hispanic skin melanocytes is probably dependent on the genetic background and not just photo protection by melanin. DNA absorbs both UVA and UVB that leads to significant alterations in its function and structure [9]. A previous study on the effect of UVR on skin from different ethnic origin suggested that in addition to the immediate UVR-induced DNA damage and mutated genes, the efficiency of DNA repair is equally important in the induction of photo carcinogenesis. Babies who were deemed to require arterial access were those in whom greater precision in respiratory or circulatory monitoring was thought to be needed. These included babies receiving significant respiratory support in whom the greater precision of arterial blood gas measurements (compared to capillary blood gas measurements) was thought to be a better guide to therapy, or babies requiring very frequent blood gas measurements, in whom repeated capillary sampling was felt to be too numerous and distressing. Other eligible babies were those requiring circulatory support with inotropes in whom the precision afforded by continuous invasive blood pressure measurement was thought be a better guide to therapy than intermittent non-invasive measurement [10, 11]. FAC insertion was performed in patients in whom arterial access was deemed to be necessary to facilitate care, as defined above, and in whom it had not proved possible to site a UAC, or a peripheral arterial catheter. The decision to site arterial access required an assessment of the benefits in the individual patient against the potential risks of the procedure. Although not specifically described in our unit policies, the threshold for femoral arterial catheter insertion was higher than the threshold for insertion of UAC or peripheral arterial catheters, with which we have greater experience [13-15].

Conclusion

One set of 4-well slides with fixed melanocytes were processed by standard histology staining protocol for HE to observe and quantify melanocytes containing MN, MLTN and PMN. Other set of 4-well slides were processed for IHC staining using our standardized protocol. Briefly, fixed melanocytes were washed in PBS, blocked in 1% BSA for 45 min, and antigen retrieved in 0.1% Triton-X for 20 min. Melanocytes were incubated overnight at 4-8°C with appropriate dilutions of primary antibody Ki67 (#9449; Cell Signaling Technology, Danvers, MA, USA; 1:400) and Cyclin D1 (sc-8396; Santa Cruz Biotechnology, Dallas, TX, USA; 1:500) as proliferation markers and p53 (sc-263; Santa Cruz Biotechnology; 1:800) as apoptotic marker.

Acknowledgement

None

Conflict of Interest

None

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