

Article

QTc intervals are prolonged in (near)term neonates during therapeutic hypothermia to normalise immediately afterwards

Karel Allegaert ^{1,2,3,*}, Thomas Salaets ⁴, Pieter Annaert ² and Anne Smits ^{1,5}

¹Department of Development and Regeneration, KU Leuven, Herestraat 49, 3000 Leuven, Belgium.

karel.allegaert@uzleuven.be (K.A.) and anne.smits@uzleuven.be (A.S.)

²Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Herestraat 49, 3000 Leuven, Belgium, pieter.annaert@kuleuven.be (P.A.).

³Department of Clinical Pharmacy, Erasmus MC, Postbus 2040, 3000 GA Rotterdam, the Netherlands.

⁴Division of Pediatric Cardiology, Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium. thomas.1.salaets@uzleuven.be

⁵Neonatal Intensive Care Unit, University Hospitals UZ Leuven, Herestraat 49, 3000 Leuven, Belgium.

* Correspondence: karel.allegaert@uzleuven.be

Abstract: Background: There are anecdotic reports on reversible QTc prolongation during therapeutic hypothermia (TH) for moderate to severe neonatal encephalopathy after asphyxia. As the QTc interval is a relevant biomarker to assess safety during medicine development, a structured search and review on published QTc values to generate reference values is warranted to facilitate medicine development in this specific population. Methods: a structured search and literature assessment (PubMed, Embase, Google Scholar) with 'Newborn/Infant, QT and hypothermia' was conducted (October 2021). Retrieved individual values were converted to QTc (Bazett) over postnatal age (day 1-7). Results: we retrieved 94 QTc intervals [during TH (n=50, until day 3) or subsequent normothermia (n=44, day 4-7)] in 33 neonates from 6 publications. The median (range) of QTc intervals during TH was 508 (430-678), and 410 (317-540) ms afterwards (difference 98 ms, or +28 ms/°C decrease). Four additional cohorts (without individual QTc intervals) confirmed the pattern and magnitude of the effect of body temperature on the QTc interval. Conclusions: we added a relevant non-maturational covariate (TH, dose dependent) and generated reference values for the QTc interval in this specific subpopulation. This knowledge on QTc during TH should be considered and integrated in neonatal medicine development.

Keywords: therapeutic hypothermia; newborn; QTc interval; QTc prolongation; pharmacovigilance

1. Introduction

Therapeutic hypothermia (TH) is the standard treatment for (near)term neonates diagnosed with moderate-to-severe hypoxic-ischemic encephalopathy (HIE) following perinatal asphyxia (PA). This intervention (target 33.5 °C, initiated before 6 hours of postnatal age and sustained for 72 h) reduces mortality and neurodevelopmental disability. Although effective with a number needed to treat (for one additional intact survival) of 7 (95% CI 5-10), there is still a relevant burden (intact survival in TH-treated versus non TH-treated, 52.4 % versus 37 %) in treated cases, so that there is an active search and imminent need for pharmacological interventions, added to TH to further improve outcome [Jacobs et al, Cochrane Database Syst Rev 2013; Allegaert et al, Curr Pharm Design 2018].

As both TH and PA affect neonatal physiology, it is reasonable to expect that this will affect clinical pharmacology (both pharmacokinetics (PK), as well as pharmacodynamics (PD), including safety)[Smits et al, Front 2020]. The efficacy and safety of a given medicine relates to the benefit-risk balance. Unfortunately, both efficacy and safety are much more difficult to establish in neonates, resulting in very few medicines licensed for use in this vulnerable population [Ward et al, Pediatr Research 2017; van den Anker Pharmaceuticals].

The QTc (c = corrected for heart rate) interval measurement and quantification of its potential prolongation has a crucial role in pharmacovigilance during medicine development. This is because it serves as an established and accepted safety indicator for ventricular repolarization disturbances and potential risk for torsade de pointes. In the absence of specific recommendations for neonatal medicine development, the existing guidance suggest to use partial extrapolation (*event and intervention are believed to behave similar in pediatric patients – including neonates – and adults, but the exposure-relationship is inadequately defined or thought not to be sufficiently similar*) as a reasonable approach [FDA; AE paper, J Clin Pharmacol 2021; Ward et al, Pediatr Research 2017].

This means that subpopulation specific information on QTc intervals during TH in (near)term neonates is relevant. At present, there are reports on the impact of TH on cardiovascular safety in the latest meta-analysis on therapeutic hypothermia, as well as in observational papers.

In the latest meta-analysis and with the focus on adverse cardiovascular effects related to TH, the incidence of hypotension (mean arterial pressure <40 mmHg) and the need for inotropics (no difference), persistent pulmonary hypertension (trend only), sinus bradycardia (heart rate <80 beats per minute (bpm), effect size 1.59, 95% CI 4.94-27.17, much more common during TH) and major arrhythmia (no difference) have been assessed on their significance and difference in incidence when compared to non TH-treated controls [Jacobs et al, Cochrane Database Syst Rev 2013]. However, no final positions were taken in this meta-analysis on 'any arrhythmia' or 'prolonged QT' interval, as insufficient data were available, while there is descriptive information in some of the original randomized controlled trials on TH retained in the meta-analysis.

In the Eicher (1998-2001) study, only data on bradycardic events (<80 bpm) were reported. These events were much more commonly observed in neonates undergoing TH (11/31 versus 2/31, 35 % versus 6 %). The National Institute of Child Health and Human Development (NICHD, 2000-2003) has not reported on the incidence of 'any bradycardia', but reported one 'persistent bradycardic event' in the TH group, and 2 events of ventricular tachycardia (one in each group). In the CoolCap (1999-2002) study, electrocardiography (ECG) data were collected in the event of a bradycardia (<80 bpm) or arrhythmia. Major cardiac arrhythmia events were not observed, minor events (almost all sinus bradycardia) were observed in 10 (9 %) of the TH-treated cases, and only 1 (1 %) in the non TH-treated controls, but data on QTc intervals were not provided. In the Infant Cooling Evaluation (ICE 2001-2007) trial, prolonged QT (definition >98th centile for heart rate and age [Davignon A et al, Pediatr Cardiol 1980]) was observed in 31 (43%) of TH-treated cases (compared to 19.7% in non-TH treated asphyxia cases), but no arrhythmias that required treatment or discontinuation of hypothermia were observed [Jacobs et al, Arch Pediatr Adolesc Med 2011]. Finally, in the Neo.Neuro study, cardiac arrhythmia (be it not clearly defined in the paper) was observed in 3/62 TH and 4/63 normothermia cases [Neo.Neuro]. Likely because of the uncertainty on the definition, the findings on this specific safety marker were not retained in meta-analysis [Jacobs et al, Cochrane Database Syst Rev 2013].

Consequently, the current meta-analytical data are rather reassuring if we focus on major arrhythmia (in need of clinical intervention), but does not provide sufficient information on the changes in QTc intervals during and after therapeutic hypothermia, while such information is relevant to assess the benefit/risk balance for pharmacological interventions, added to TH to further improve outcome. Besides its relevance for medicine development, there is also diagnostic relevance, as a very recent case report in this journal described the postnatal management of a newborn with a congenital long QT syndrome (genetic mutation, SCN5A gene documented during later stay), presenting with ventricular fibrillation at birth, but subsequently also underwent TH because of HIE [Mileder et al, Children 2021]. In such a scenario, one should be able to compare QTc intervals collected during TH to reference values in this specific setting.

We therefore conducted a structured search and review on reported QTc intervals in this specific TH population (during TH, and afterwards) to generate such reference values.

2. Materials and Methods

A structured search was performed in October 2021 in PubMed, Google Scholar and Embase, with the combination “Newborn or Infant, hypothermia and QT”. All hits were screened on title and abstract by one author (K.A.) to assess on potential relevance to the topic. If perceived to be of relevance, the full paper was read. If retained for the analysis, both references and citations were further checked for potential other relevant papers. There were no predefined language restrictions (besides the search strategy, English terms). The clinical studies retained in the latest meta-analysis on therapeutic hypothermia were also screened, using the same approach of reference and citation screening [Jacobs et al, Cochrane Database Syst Rev 2013].

Data as reported in the individual papers were collected as individual observations (either paired, or unpaired). When needed, individual observations plotted in figures were extracted using specific software (WebPlot Digitizer, by Ankit Rohatgi, <https://automeris.io/WebPlotDigitizer/>). In the event that QT and heart rate were reported, data were converted to QTc (Bazett) based on the formula $[QTc\text{ (ms)} = QT / \sqrt{RR\text{ interval}}]$. All data were reported in ms. Statistics were descriptive (median and range, or mean and standard deviation), compared QTc (Bazett) time during and after TH (unpaired t-test), or explored trends over postnatal age (days) in both time intervals (TH, afterwards during normothermia) (MedCalc®, Ostend, Belgium).

3. Results

The initial search in PubMed on ‘Newborn or Infant’, ‘hypothermia’ and ‘QT’ resulted in 6 and 9 hits (newborn and infant, respectively). The same Embase search resulted in 22 and 22 hits. A Google Scholar search (including citations) resulted in 11 200 and 12 200 hits. The first 500 hits (priority listed) were screened on relevance.

Following the approach described, and combining cohorts and single cases reported, we retrieved individual QTc intervals during TH (n=50, up to day 3) and afterwards (n = 44, day 4-7)(Figure 1) in 33 individual neonates. The largest dataset contained 37 and 39 QTc intervals during and after TH respectively, collected in 19 neonates [Vega]. A second dataset reported on 10 QTc intervals in 10 cases during TH [Battin]. The data in both cohorts were further extended by 4 individual cases (5 QTc intervals during TH, 3 afterwards) [Blengio, Rockefeller, Farneschi, Gunn]. In almost all cases, the QTc interval prolongations were documented during clinical care, and accepted without additional clinical interventions. However, in the Blengio case, the temperature was raised from 33.5 °C to 34.5 °C with subsequent continuation (QTc interval from 619 to 480 ms, afterwards during normothermia 317 ms). In the Farneschi case (late preterm, 34 weeks, 6 days), the QTc interval during TH was 581 ms, and the clinical decided to stop TH in this specific case.

Figure 1 provides the individual QTc intervals as published over postnatal age in the first week of life, with the first 3 days during TH, and up to postnatal day 7 afterwards (normothermia). The median (range) of the QTc interval during TH was 508 (430-678) ms. Afterwards, it was 410 (317-540) ms, so that the difference between both settings is 98 ms, or assuming a temperature difference between both setting of 3.5 °C, +28 ms/ °C decrease. During TH, 27/50 QTc intervals were >500 ms, and even 20/50 were >520 ms. We could not document a significant trend over postnatal age over the TH time interval (day 1-3) or in the time interval (day 4-7) afterwards. However, a mixed model approach was not possible and only unpaired analysis could be done, as the data as published in the literature did not allow to disentangle paired and unpaired observations.

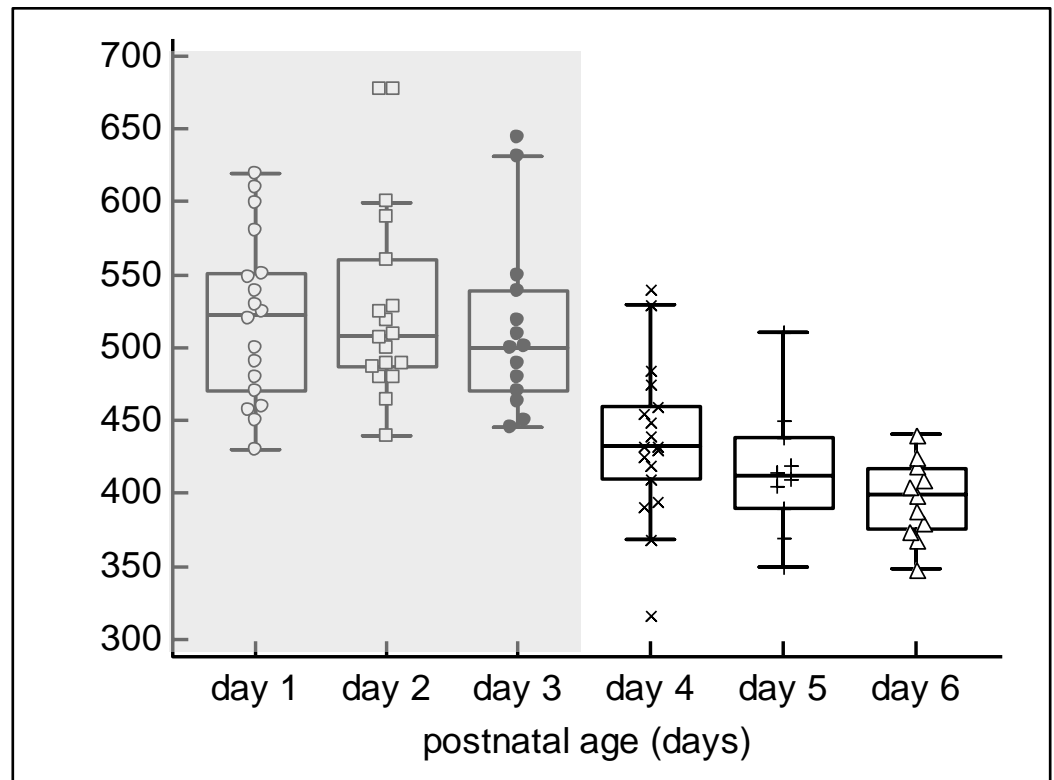


Figure 1. Pooled individual QTc intervals over postnatal age with 94 observations in 33 neonates. (day 1-3: therapeutic hypothermia (light grey); day 4-7: normothermia, white) [Vega, Battin, Blengio, Rockefeller, Farneschi, Gunn]. de

Besides these individual observations, we further retrieved 4 cohorts relevant to the topic, all with focus on QTc 'temperature-time interval' prolongation. Cavallaro et al. compared differences in cardiovascular parameters between moderate (33.5 °C) and deep hypothermia (31 °C). The authors observed that 2/14 and 3/31 had a QTc interval >520 ms during mild and deep hypothermia respectively [Cavallaro et al, ISRN Pediatr 2013]. Horan et al. quantified the mean difference in QTc interval from 37 to 34 °C (431, 459, 445 and 465 ms at 37, 36, 35 and 34 °C respectively) in 27 neonates undergoing TH while receiving extracorporeal membrane oxygenation (ECMO), and suggested a 3.12 ms increase/ °C decrease [Horan et al, Early Human Develop 2007]. Lasky et al. also recorded QTc interval in 2 HIE newborns during TH and subsequent rewarming. For each increment of 1 °C during rewarming, there was an increase of 9.2 bpm in heart rate, and a QTc interval decrease by 21.6 ms [Lasky et al, Neonatology]. Finally, Montaldo et al. associated a longer QTc and longer RR interval (lower heart rate) during TH with subsequent better neurodevelopmental outcome at 18-24 months in a cohort of 64/73 survivors (44/64 were classified with a normal neurodevelopment outcome) [Montaldo et al, Resuscitation 2018]. Based on paired data analysis following repeated QTc intervals before (admission), during TH (12, 24, 36, 48, 60, 72 h) and subsequent normothermia in this cohort, the authors described a progressive increase in QTc intervals up to 36-48 h, with a subsequent decrease already during TH to normalize after rewarming [Montaldo et al, Resuscitation 2018].

4. Discussion

Using a structured assessment and pooling of the available individual QTc intervals as reported in literature, we constructed a pattern of reference values for QTc in (near)term neonates during TH and immediately afterwards. This pattern shows a significant (and from a pharmacovigilance perspective, a highly relevant) increase on QTc interval during TH, with subsequent normalization shortly afterwards. This pattern based

on individual measurements reported by 6 different groups confirms the Montaldo cohort pattern, based on rich sampling in a single cohort in one unit [Montaldo, Resuscitation]. This increase in QTc is 'dose dependent', when quantified by incremental changes in temperature ($^{\circ}\text{C}$). Based on the differences in median QTc interval during TH and afterwards (normothermia), it was estimated to be $+28\text{ ms}/^{\circ}\text{C}$ decrease, similar to the observation during rewarming in 2 cases ($21.6\text{ ms}/^{\circ}\text{C}$) [Lasky et al, Neonatology]. In contrast, but in an ECMO setting that in itself affects hemodynamics, this was estimated only to be $3.12\text{ ms}/^{\circ}\text{C}$ [Horan et al, Early Human Development 2007]. Despite this relevant, dose dependent increase during TH, this is only very rarely associated with 'major arrhythmia', except for sinus bradycardia, so that the findings are mainly important for pharmacovigilance or diagnostic purposes.

Interestingly, these findings in human neonates were also observed in pre-clinical juvenile animal studies. Furthermore, and from a pharmacovigilance approach, we should reflect on how to handle and integrate these 'phenotypic findings' into neonatal medicine development programs for this specific TH subpopulation [Matcha et al, *Pediatr Res* 2021; Ward et al, *Pediatr Res* 2018; Smits et al, *Front Pharmacol* 2020].

Kerenyi et al. explored the dose-effect relationship of whole-body cooling (normothermia, to 35 to 33.5 to 30°C respectively) in a piglet model of perinatal asphyxia. In this asphyxia model, 'inadvertent' overcooling to 30°C commonly resulted in metabolic derangements, cardiac arrests and death (5/7 animals) [Kerenyi et al, *Pediatr Res*]. QTc interval prolongation has also been reported in the swine model (from normothermia to 32°C , median QTc interval increased from 376 to 570 ms). However, mild TH was not associated with an increased success to induce ventricular fibrillation, but rather (in normokalemia setting) exerted an anti-arrhythmic effect despite the prolonged QTc interval [Kudlicka et al, *J Transl Med* 2015]. A similar pattern of QTc interval prolongation has also been described in the dog, both during artificial cooling or warming (range 34.2 - 42.1°C) when compared to controls (beagle dog: median QTc interval: control 264 , versus cooled 269 or heated 259 ms respectively).

Although these data are relevant to neonatal medicine development, is it still uncertain how to integrate these findings into medicine development practices. This pharmacovigilance practice has been introduced after medicine-induced arrhythmias were identified as the cause of syncope associated with quinidine [Lester RM et al, *Int J Mol Sci*, PMID 30884748]. Following this pivotal observation, an extensive list of medicines that prolong the QTc interval emerged, and potential synergisms (either PK, or PD mediated) has been constructed [Arizona univ]. From a regulatory perspective, regulations were developed for "thorough QT/QTc studies". Subsequent revisions reflected on how to evaluate medicine-induced changes in QT when a "thorough QT/QTc study in healthy volunteers" cannot be conducted for safety related issues [FDA guidance, Guidance for Industry: E14].

Unrelated to the 'volunteer' construct that is by default not applicable to neonates, it is still a matter of debate how this 'QT/QTc pharmacovigilance' practice should be applied in neonatal pharmacotherapy and medicine development in this population. Besides study design, there are also maturational changes in the QTc interval that should be considered. Ulrich reported on maturational changes in QTc interval in 114 (pre)term neonates in the first week of life (range 31 - ≥ 37 weeks gestational age). Irrespective of the gestational age, there was a progressive shortening of the QTc interval with increasing postnatal age, while the initial QTc intervals at birth were in part determined by the gestational age (mean QTc interval of 475 , 452 and 444 ms in 31 - <34 weeks, 34 - <37 weeks and ≥ 37 weeks respectively) [Ulrich et al, *Pediatr Cardiol* 2014]. Based on the current analysis, we added a relevant non-maturational covariate (TH as intervention, dose dependent) to this pattern, somewhat in line with the PD effect of TH on seizure control ('thermopharmacology') [van den Broek et al, *Clin Pharmacokinet* 2012; Allegaert et al, *Eur J Pharm Sci* 2017].

There are reports on QTc interval prolongation assessment for medicines known to affect the QTc interval in adults before and following exposure in neonates, like for e.g.

cisapride (in both cohorts resulting in prolongation of the QTc interval, dose dependent, in both preterm and term neonates, + 20 ms) [Cools et al, Eur J Clin Pharmacol 2003; Zamora et al, Biol Neonate 2001] or domperidone (no effect on mean QTc interval) [Günlemez et al, J Perinatol 2010], but it remains difficult to put this into perspective, especially for medicines assessed in the first week of life or during TH because of the maturational and non-maturational changes. In the absence of robust guidance at present, we suggest that in vitro (hERG) or in vivo (healthy volunteers) screening are considered, pending feasibility [Strauss DG et al, Clin Pharmacol Ther 2021]. Vargas et al. recently suggest that a double negative non-clinical data (negative in vitro human ether-a-go-go-related gene (hERG) + in vivo heart-rate corrected QTc assays are associated with such a low probability of clinical QTc interval prolongation and medicine-induced torsade de pointes that 'double' negative medicines would subsequently not need detailed clinical QTc interval evaluation [Strauss DG et al, Clin Pharmacol Ther 2021; Graaf et al, CPT]. This approach could likely be even more relevant for medicine development program focused in early neonatal life, as in vivo phenotypic assessment will have major limitations to recognize a potential relevant signal in the noise of extensive inter- and intra-patient variability, even more during TH.

5. Conclusions

A pattern of reference values for the QTc interval in (near)term neonates during TH and immediately afterwards has been constructed, and reflects a dose dependent, reversible effect on the QTc interval (+28 ms/ °C decrease), with a median (range) of 508 (430-678) ms during TH. Consequently, we have added a relevant non-maturational covariate (TH as intervention, dose dependent) to the existing maturational pattern of QTc interval in early neonatal life. This knowledge on QTc interval variability should be considered and integrated in neonatal medicine development, including in neonates undergoing TH.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, K.A.; methodology, K.A.; resources, K.A, P.A, A.S.; writing—original draft preparation, K.A.; writing—review and editing, K.A, T.S., P.A., A.S.; funding acquisition, K.A., P.A., A.S. All authors have read and agreed to the published version of the manuscript." Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

Funding: This research was funded by FWO Vlaanderen (iPREDICT, FWO Senior research project, fundamental research, GOD0520N).

Institutional Review Board Statement: not applicable

Conflicts of Interest: The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Jacobs, S.E.; Berg, M.; Hunt, R.; Tarnow-Mordi, W.O.; Inder, T.E.; Davis, P.G. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst. Rev.* **2013**, 2013, CD003311. doi:10.1002/14651858.CD003311.pub3.
2. Allegaert, K.; Smits, A.; Simons, S.; van den Anker, J. Perspectives in neonatal pharmacology: drug discovery, knowledge integration and structured prioritization. *Curr. Pharm. Des.* **2018**, 24, 4839-4841. doi:10.2174/13816128244190320125910.
3. Smits, A.; Annaert, P.; Van Cruchten, S.; Allegaert, K. A physiology-based pharmacokinetic framework to support drug development and dose precision during therapeutic hypothermia in neonates. *Front. Pharmacol.* **2020**, 11, 587. doi:10.3389/fphar.2020.00587.
4. Ward, R.M.; Benjamin, D.; Barrett, J.S.; Allegaert, K.; Portman, R.; Davis, J.M.; Turner, M.A. Safety, dosing, and pharmaceutical quality for studies that evaluate medicinal products (including biological products) in neonates. *Pediatr. Res.* **2017**, 81, 692-711. doi: 10.1038/pr.2016.221.
5. Van den Anker, J.N.; McCune, S.; Annaert, P.; Baer, G.R.; Mulugeta, Y.; Abdelrahman, R.; Wu, K.; Krudys, K.M.; Fisher, J.; Slikker, W.; et al. Approaches to dose findings in neonates, illustrating the variability between neonatal drug development programs. *Pharmaceutics*, **2020**, 12, 685. doi: 10.3390/pharmaceutics12070685.
6. Allegaert, K.; van den Anker, J. Dose-related adverse drug events in neonates: recognition and assessment. *J. Clin. Pharmacol.* **2021**, 61 (Suppl 1), S152-S160. doi: 10.1002/jcph.1827.

7. United States Food and Drug Administration. FDA Center for Drug Evaluation of Research (CDER). General clinical pharmacology considerations for pediatric studies for drugs and biological products. Guidance for industry. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-and-biological-products> (accessed on 29 October 2021).
8. Davignon, A. Normal ECG standards for children. *Pediatr. Cardiol.* **1980**, *1*, 133-152. doi:10.1007/BF02083145.
9. Jacobs, S.E.; Morley, C.J.; Inder, T.E.; Stewart, M.J.; Smith, K.R.; McNamara, P.J.; Wright, I.M.; Kirpalani, H.M.; Darlow, B.A.; Doyle, L.W.; Infant Cooling Evaluation Collaboration. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. *Arch. Pediatr. Adolesc. Med.* **2011**, *165*, 692-700. doi:10.1001/archpediatrics.2011.43.
10. Simbruner, G.; Mittal, R.A.; Rohlmann, F.; Muche, R.; neo.nEURO.network trial participants. Systemic hypothermia after neonatal encephalopathy: outcomes of the neo.nEURO.network RCT. *Pediatrics* **2010**, *126*, e771-e778. doi:10.1542/peds.2009-2441.
11. Miledner, L.P.; Morris, N.M.; Kurath-Koller, S.; Pansy, J.; Pichler, G.; Pocivalnik, M.; Schwabegger, B.; Burmas, A.; Urlesberger, B. Successful postnatal cardiopulmonary resuscitation due to defibrillation. *Children* **2021**, *8*, 421. doi:10.3390/children8050421.
12. Rohatgi, A. Available online: <https://automeris.io/WebPlotDigitizer> (accessed on 29 October 2021).
13. Vega, L.; Boix, H.; Albert, D.; Delgado, I.; Castillo, F. Corrected QT interval during therapeutic hypothermia in hypoxic ischaemic encephalopathy. *An. Pediatr. (Barc.)* **2016**, *85*, 312-317. doi:10.1016/j.anpedi.2016.01.006.
14. Battin, M.R.; Penrice, J.; Gunn, T.R.; Gunn, A.J. Treatment of term infants with head cooling and mild systemic hypothermia (35.0 °C and 34.5 °C) after perinatal asphyxia. *Pediatrics* **2003**, *111*, 244-251. doi:10.1542/peds.111.2.244.
15. Blengio, A.; Pose, G. Prolongation of the QT interval during therapeutic hypothermia in a newborn with hypoxic-ischemic encephalopathy: a case report. *Arch. Pediatr. Urug.* **2021**, *92*, e301. doi:10.31134/AP.92.1.6.
16. Rockefeller, T.A.; Silva, J.N.; Liao, S.; Vachharajani, A. Corrected QT prolongation and bradycardia during therapeutic hypothermia in an infant. *Neoreviews* **2016**, *17*, e40. doi:10.1542/neo.17-1-e40.
17. Farneschi, L.; Mori, A.; Tataranno, M.L.; Muraca, M.C.; Rodriguez, D.C.; Giomi, S.; Coviello, C.; Buonocore, G. Therapeutic hypothermia in a late preterm infant. *J. Matern. Fetal Neonatal Med.* **2012**, *25* (suppl 1), 125-127. doi:10.3109/14767058.2012.663172.
18. Gunn, T.R.; Wilson, N.J.; Aftimos, S.; Gunn, A.J. Brain hypothermia and QT interval. *Pediatrics* **1999**, *103*, 1079. doi:10.1542/peds.103.5.1079.
19. Cavallaro, G.; Filippi, L.; Raffaelli, G.; Cristofori, G.; Schena, F.; Agazzanin, E.; Amodeo, I.; Griggo, A.; Boccassi, S.; Fiorini, P.; Mosca, F. Heart rate and arterial pressure changes during whole-body deep hypothermia. *ISRN Pediatr.* **2013**, *2013*, 140213. doi:10.1155/2013/140213.
20. Horan, M.; Edwards, A.D.; Firmin, R.K.; Ablett, T.; Rawson, H.; Field, D. The effect of temperature on the QTc interval in the newborn infant receiving extracorporeal membrane oxygenation (ECMO). *Early Hum. Dev.* **2007**, *83*, 217-223. doi:10.1016/j.earlhumdev.2006.05.016.
21. Lasky, R.E.; Parikh, N.A.; Williams, A.L.; Padhye, N.S.; Shankaran, S. Changes in the PQRST intervals and heart rate variability associated with rewarming in two newborns undergoing hypothermia therapy. *Neonatology* **2009**, *96*, 93-95. doi:10.1159/000205385.
22. Montaldo, P.; Cuccaro, P.; Caredda, E.; Pugliese, U.; De Vivo, M.; Orbinato, F.; Magri, D.; Rojo, S.; Rosso, R.; Santantonio, A.; et al. Electrocardiographic and echocardiographic changes during therapeutic hypothermia in encephalopathic infants with long-term adverse outcome. *Resuscitation*, **2018**, *130*, 99-104. doi:10.1016/j.resuscitation.2018.07.014.
23. Matcha, S.; Raj, E.A.; Mahadevan, R.; Raju, A.P.; Rajesh, V.; Lewis, L.E.; Mallayasamy, S. Pharmacometric approach to assist dosage regimen design in neonates undergoing therapeutic hypothermia. *Pediatr. Res.*, **2021** online. doi:10.1038/s41390-021-01714-0.
24. Kerenyi, A.; Kelen, D.; Faulkner, S.D.; Bainbridge, A.; Candrasekaran, M.; Cady, E.B.; Golay, X.; Robertson, N.J. Systemic effects of whole-body cooling to 35 °C, 33.5 °C, and 30 °C in a piglet model of perinatal asphyxia: implications for therapeutic hypothermia. *Pediatr. Res.* **2012**, *71*, 573-582. doi:10.1038/pr.2012.8.
25. Kudlicka, J.; Mlcek, M.; Belohlavek, J.; Hala, P.; Lacko, S.; Janak, D.; Havranek, S.; Malik, J.; Janota, T.; Ostadal, P.; et al. Inducibility of ventricular fibrillation during mild therapeutic hypothermia: electrophysiological study in a swine model. *J. Transl. Med.* **2015**, *13*, 72. doi:10.1186/s12967-015-0429-9.
26. Lester, R.M.; Paglialunga, S.; Johnson, I.A. QT assessment in early drug development: the long and the short of it. *Int. J. Mol. Sci.* **2019**, *20*, 1324. doi:10.3390/ijms20061324.
27. Center of Education and Research in Therapeutics of the University of Arizona (AzCERT). Risk categories for drugs that prolong QT and induce torsades de pointes (TdP) <https://www.crediblemeds.org/index.php/druglist> (accessed on 29 October 2021).
28. United States Food and Drug Administration. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinical-evaluation-qtqt-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-0> (accessed on 29 October 2021).
29. Ulrich, T.J.; Ellsworth, M.A.; Caey, W.A.; Zubair, A.S.; MacQueen, B.C.; Colby, C.E.; Ackerman, M.J. Heart-rate-corrected QT interval evolution in premature infants during the first week of life. *Pediatr. Cardiol.* **2014**, *35*, 1363-1369. doi:10.1007/s00246-014-0937-z.

-
30. Van den Broek, M.P.; Groenendaal, F.; Toet, M.C.; van Straaten, H.L.; van Hasselt, J.G.; Huitema, A.D.; de Vries, L.S.; Egberts, A.C.; Rademaker, C.M. Pharmacokinetics and clinical efficacy of phenobarbital in asphyxiated newborns treated with hypothermia: a thermopharmacological approach. *Clin. Pharmacokinet.* **2012**, *51*, 671-679. doi:10.1007/s40262-012-0004-y.
 31. Allegaert, K.; Simons, S.H.P.; Tibboel, D.; Krekels, E.H.; Knibbe, C.A.; van den Anker, J.N. Non-maturational covariates for dynamic systems pharmacology models in neonates, infants, and children: Filling the gaps beyond developmental pharmacology. *Eur. J. Pharm. Sci.* **2017**, *109S*, S27-S31. doi:10.1016/j.ejps.2017.05.023.
 32. Cools, F.; Benatar, A.; Bruneel, E.; Theyskens, C.; Bougatef, A.; Casteels, A.; Vandenplas, Y. A comparison of the pharmacokinetics of two dosing regimens of cisapride and their effects on corrected QT interval in premature infants. *Eur. J. Clin. Pharmacol.* **2003**, *59*, 17-22. doi:10.1007/s00228-003-0582-6.
 33. Zamora, S.A.; Belli, D.C.; Friedli, B.; Jaeggi, E. 24-hour electrocardiogram before and during cisapride treatment in neonates and infants. *Biol. Neonate* **2004**, *85*, 229-236. doi:10.1159/000076237.
 34. Günlemez, A.; Babaoğlu, A.; Arisoy, A.E.; Türker, G.; Gökalp, A.S. Effect of domperidone on the QTc interval in premature infants. *J. Perinatol.* **2010**, *30*, 50-53. doi:10.1038/jp.2009.96.
 35. Strauss, D.G.; Wu, W.W.; Li, Z.; Koerner, J.; Garnett, C. Translational models and tools to reduce clinical trials and improve regulatory decision making for QTc and proarrhythmia risk (ICH E14/S7B Updates). *Clin. Pharmacol. Ther.* **2021**, *109*, 319-333. doi:10.1002/cpt.2137.
 36. van der Graaf, P.H. Toward replacement of thorough QT studies. *Clin. Pharmacol. Ther.* **2021**, *109*, 281-282. doi:10.1002/cpt.2136