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Haemodynamics of intravenous paracetamol in neonates

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3 ***Haemodynamics of intravenous paracetamol in neonates***
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3 1 **Abstract**
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9 3 Introduction: Haemodynamics of intravenous (iv) paracetamol in adult intensive care were recently
10 4 published. We therefore wanted to explore haemodynamics of iv paracetamol in neonates.
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13 5 Methods: Retrospective, pooled analysis of heart rate (bpm) and blood pressure (mean, systolic,
14 6 diastolic) observations collected during iv paracetamol pharmacokinetic studies in neonates. Heart
15 7 rate and blood pressure were recorded just before and 30, 60, 120, 180, 240, 300 and 360 minutes
16 8 after iv paracetamol (paired, ANOVA). Clinical characteristics in hypotensive (mean mmHg <
17 9 gestational age, weeks) cases were compared with controls (Mann Whitney U).
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26 10 Results: Based on observations in 72 neonates, heart rate decreased from 145 (SD 20) to 138 (21),
27 11 141(20), 137(20), 137(22), 140(20), 139(20) and 140(21) bpm (paired $p < 0.05$, ANOVA $p = 0.36$). There
28 12 were no changes in systolic and diastolic pressure, but mean arterial pressure decreased from 46 (7)
29 13 to 43(8) mmHg at 60 minutes (paired $p < 0.05$, ANOVA $p = 0.75$). Eight neonates developed
30 14 hypotension. These cases had lower pre-administration arterial pressure (38 vs 47 mmHg, $p < 0.05$).
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39 15 Conclusions: In a setting of open label administration to alleviate (procedural) pain, haemodynamic
40 16 effects of iv paracetamol in neonates remained modest. We do suggest to consider impaired
41 17 haemodynamics to be a relative contra-indication for iv paracetamol in neonates.
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26 Introduction

27 Paracetamol (acetaminophen) is the most frequently prescribed drug for pain or fever, also in
28 neonates and can be administered by oral, rectal or intravenous (iv) route. An iv formulation likely
29 improves prediction of concentration compared to enteral formulations by elimination of absorption
30 variability. In recent years, data on iv paracetamol pharmacokinetics were described [1-3]. In
31 contrast, data on the pharmacodynamics of this formulation in neonates are unreported.

32 de Maat *et al.* recently published their observations with iv paracetamol in adult medium and
33 intensive care [4]. The authors illustrated that iv paracetamol affects haemodynamics (i.e. induces
34 hypotension) in critically ill adults. They hereby confirmed other reports on haemodynamic (side)-
35 effects of this drug in critically ill adults [5-7]. Since clinical characteristics, co-morbidity and
36 pharmacodynamics may be different in adults compared to neonates, we decided to quantify
37 haemodynamics following iv paracetamol in neonates, based on pooled data analysis of observations
38 collected during a reported pharmacokinetic study [1] and an ongoing study on pharmacokinetics
39 and -dynamics of iv paracetamol (PARANEO, NCT 00969176).

40 Methods

41 Available cohorts

42 *Single dose pharmacokinetic study in neonates* [1]

43 Neonates admitted within 24 hours after birth and with an arterial line were included if
44 propacetamol (Prodafalgan®, Bristol Myers Squibb, Braine l'Alleud, Belgium) was administered.
45 Propacetamol is iv prodrug of paracetamol but necessitates plasma esterase activity. This esterase
46 function is already at adult level of activity in early life [3]. Propacetamol was administered when
47 neonates underwent minor, painful procedures (e.g. insertion of peripheral arterial or venous line,
48 insertion of central venous line, placement of chest tube) or as additional therapy in neonates on
49 opioids. The decision to prescribe propacetamol or any other analgesic was made by the attending

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3 50 neonatologist. Exclusion criteria were major congenital malformations or birth asphyxia (Apgar < 4 at
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5 51 5 minutes). In this study, 30 patients were included. In the first 15 patients, 20 mg (equal to 10 mg
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8 52 paracetamol)/kg was administered, in the next 15 patients, 40 mg (equal to 20 mg paracetamol)/kg.
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10 53 Mean birth weight was 2111 (SD 1094) g, mean gestational age (GA) was 33.8 (SD 3.9) weeks. Mean
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12 54 postnatal age was 12.7 (SD 6.4) h. 10 neonates were term, 20 were preterm (<37 weeks GA), of
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15 55 whom 10 <32 weeks GA [1].
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18 56 *Repeated dose PK/PD study* (PARANEO, NCT 00969176, www.clinicaltrials.gov).
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20
21 57 Interim analysis of a still ongoing study on pharmacokinetics, -dynamics and safety of repeated iv
22
23 58 paracetamol administration in the 42 neonates currently included. Indications for initiation of iv
24
25 59 paracetamol were medical or surgical painful conditions [8]. Mean weight was 2580 (SD 890) g, mean
26
27 60 gestational age (GA) 35.5 (SD 4.4) weeks, mean postnatal age 3 (range 1-27) days. Twenty-two
28
29 61 neonates were term, 20 preterm (<37 weeks GA), of whom 4 < 32 weeks GA. Primary outcome of this
30
31 62 ongoing study are iv paracetamol pharmacokinetics, but pharmacodynamics - including
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33 63 haemodynamics – are also collected. The dosing regimen is based on a loading dose (20 mg/kg
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35 64 paracetamol), followed by an age dependent maintenance dose (5 to 10 mg/kg/6h) [2].
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40 65 2. Haemodynamics

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43 66 Individual patient files were analysed for data on blood pressure [mean, systolic, diastolic (mmHg)]
44
45 67 and heart rate (beats/min) from just before the first administration of iv paracetamol until 6 hours
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47 68 after iv paracetamol administration. We hereby focused on hemodynamic effects of the first dose.
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49 69 Besides absolute values (mmHg), any mean arterial blood pressure < GA for a given GA (e.g. neonate
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51 70 of 30 weeks should have a mean arterial blood pressure of at least 30 mmHg) was recorded since this
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53 71 is the most frequently used, 'bedside' indicator of hypotension in neonates [8]. All observations are
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55 72 based on intra-arterial measurements.
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60 73 3. analysis and statistics

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3 74 For statistical analysis, Medcalc® (Mariakerke, Belgium) was used. From the individual data, mean
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5 75 values and standard deviation were calculated when normal distribution was documented
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8 76 (Kolmogorov-Smirnov test), otherwise data are reported by median and range.

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10 77 Baseline haemodynamics were recorded just before iv paracetamol administration. Correlations
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12 78 (spearman rank) between baseline values (heart rate, mean arterial blood pressure) and clinical
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14 79 characteristics (weight, age) were explored. Compared to baseline haemodynamics, changes in
15
16 80 parameters up to 6 h after iv paracetamol were collected. From these individual data, mean values
17
18 81 were calculated. Paired Wilcoxon was subsequently used to analyze changes compared to baseline
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20 82 (bpm, mmHg). One-way analysis of variance (ANOVA) was applied to test differences between the
21
22 83 means of consecutive measurements. Finally, incidence of hypotension was calculated, and
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24 84 characteristics of neonates who developed hypotension (any time) following iv paracetamol were
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26 85 compared with normotensive cases (Mann Withney-U).

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Results

The pooled dataset consisted of haemodynamics in 72 patients and both preterm (n=40) and term (n=32) neonates were included. Baseline mean, systolic and diastolic blood pressure before iv paracetamol were 46 (SD 7), 55 (SD 10) and 38 (7) mmHg, baseline heart rate was 145 (SD 20) bpm. Significant correlations between age and mean blood pressure ($r = -0.39$, $p < 0.01$) or heart rate ($r = 0.28$, $p < 0.05$) were documented, reflecting the relative lower mean arterial pressure and higher heart rate in the smallest neonates.

Consecutive observations (mean, SD) on heart rate and mean, systolic and diastolic blood pressure are provided in table 1. There was a significant decrease (paired analysis) in heart rate 30 (-7 bpm), 60 (-4 bpm) and 120 (-8 bpm) (all at least $p < 0.05$) minutes following iv paracetamol with a subsequent trend towards normalization but still remaining significantly lower (all $p < 0.05$) up to 360 minutes afterwards. Using ANOVA, there were no significant differences in the consecutive measurements ($p = 0.36$). Mean arterial blood pressure displayed a minor, statistically significant decrease (-3 mmHg) at 60 minutes, with subsequent return to baseline values, without alterations in systolic or diastolic blood pressure. Similarly, there were no significant differences in mean arterial pressures using ANOVA ($p = 0.75$).

Still 18 observations in 8 (9 %) neonates were below the threshold of normal mean arterial blood pressure, defined as below the mmHg for the given age at inclusion. When clinical characteristics of hypotensive (n=8) were compared with normotensive (n=64) cases, there was no significant difference in age (35 vs 36 weeks) or weight (2455 vs 2425 g), but baseline mean arterial pressure (38 vs 47 mmHg, $p < 0.05$) was already lower in cases who subsequently developed hypotension. Baseline heart rate was not significantly different (154 vs 142 bpm).

124 **Discussion**

125 Based on prospectively collected observations in 72 neonates, we observed a clinical modest
126 decrease in heart rate (7bpm) and mean arterial blood pressure (3mmHg) following iv paracetamol
127 administration. A minority (9 %) developed hypotension. Interestingly, these neonates already had
128 significantly lower blood pressure before paracetamol administration.

129 Effective management of pain should be based on systematic assessment of pain, followed by
130 titrated administration of the most appropriated analgesic(s) with subsequent re-assessment. In any
131 patient, the administration of an analgesic is a balanced decision based on perceived benefits (e.g.
132 agitation, pain, stress) and risks (e.g. hypotension, bowel paresis, hypersensitivity, intolerance,
133 withdrawal, neuro-apoptose) [9]. When we focus on the haemodynamics of analgesics or sedatives
134 in neonates, there are observations on effect of midazolam (+30 bpm, -3 mmHg)[10], fentanyl (-13
135 bpm, - 3 mmHg) [11], fentanyl and midazolam (- 19 bpm, - 12 mmHg)[12], propofol (-9 bpm, -14
136 mmHg)[13] or morphine (-8 bpm, -3 mmHg)[14,15] on heart rate and mean arterial blood pressure.
137 Pre-existing low mean arterial pressure was as risk factor for subsequent hypotension following
138 morphine administration [15].

139 The present observations following iv paracetamol in neonates are likely the phenotypic result of
140 both improved analgesia and procedural (initial indication for iv paracetamol) related effects and one
141 should take into account that paracetamol was administered unblinded and the pooled analysis was
142 retrospective. Taking these weaknesses into account, we suggest that -compared to other analgesics
143 or sedatives, haemodynamic changes following iv paracetamol are limited, but not absent [11-16]. It
144 seems cautious to consider preadministration impaired haemodynamics a relative contra-indication
145 to initiate iv paracetamol.

146 We can't but speculate why haemodynamics of iv paracetamol seems to be different in neonates
147 [5,7]. Hersch *et al.* [7] suggested that (traumatic) brain injury and pyrexia/hyperthermia are risk
148 factors while de Maat *et al.* [5] were unable to unveil risk factors in medium- and intensive care adult

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3 149 patients. At least, it was illustrated that focused studies on pharmacokinetics and -dynamics in
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5 150 neonates are relevant [16].
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For Peer Review

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Table 1

Haemodynamics of iv paracetamol in 72 neonates. Heart rate and blood pressure (mean, systolic, diastolic) reported by mean and standard deviation for all consecutive time intervals.

	Pre	30 min	60 min	120 min	180 min	240 min	300 min	360 min
Heart rate (bpm)	145 (20)	138 (21)	141 (20)	137 (20)	137 (22)	140 (20)	139 (20)	140 (21)
Blood pressure								
Mean (mmHg)	46 (7)	45 (7)	43 (8)	45 (8)	44 (7)	45 (8)	45 (8)	45 (8)
Systolic (mmHg)	55 (10)	52 (8)	51 (9)	53 (10)	51 (9)	53 (10)	51 (9)	52 (9)
Diastolic (mmHg)	38 (7)	39 (7)	38 (8)	39 (8)	38 (7)	39 (8)	37 (7)	39 (8)

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3 ***Haemodynamic effects of intravenous paracetamol in (pre)term neonates***
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41 1 table
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3 1 **Abstract**
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9 3 Introduction: Haemodynamics of intravenous (iv) paracetamol in adult intensive care were recently
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11 4 published. We therefore wanted to evaluate haemodynamics of iv paracetamol in neonates.
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14 5 Methods: Pooled analysis of data on heart rate (bpm) and blood pressure (mean, systolic, diastolic)
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16 6 collected during iv paracetamol pharmacokinetic studies in neonates. Heart rate and blood pressure
17
18 7 were recorded just before and 30, 60, 120, 180, 240, 300 and 360 minutes after iv paracetamol
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20 8 (paired, ANOVA). Clinical characteristics in hypotensive (mean mmHg < gestational age, weeks) cases
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22 9 were compared with controls (Mann Whitney U).
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25

26 10 Results: Based on observations in 72 neonates, heart rate decreased from 145 (SD 20) to 138 (21),
27
28 11 141(20), 137(20), 137(22), 140(20), 139(20) and 140(21) bpm (paired $p < 0.05$, ANOVA $p = 0.36$). There
29
30 12 were no changes in systolic and diastolic pressure, but mean arterial pressure decreased from 46 (7)
31
32 13 to 43(8) mmHg at 60 minutes (paired $p < 0.05$, ANOVA $p = 0.75$). Eight neonates developed
33
34 14 hypotension. These cases had lower pre-administration arterial pressure (38 vs 47 mmHg, $p < 0.05$).
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39 15 Conclusions: Although these data were collected following unblinded administration to alleviate
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41 16 (procedural) pain, it seems that haemodynamic effects iv paracetamol are modest (-8 bpm, -3
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43 17 mmHg mean arterial pressure). We suggest to consider impaired haemodynamics a relative contra-
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45 18 indication for iv paracetamol in neonates.
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26 Introduction

27 Paracetamol (acetaminophen) is the most often prescribed drug for mild to moderate pain or fever in
28 children, including neonates and can be administered by oral, rectal or intravenous (iv) route. An iv
29 formulation likely improves prediction of concentration and effect compared to enteral formulations
30 by elimination of absorption variability. In recent years, data on iv paracetamol pharmacokinetics
31 were described [2,3,4]. In contrast, data on the pharmacodynamics of this formulation in neonates
32 are unreported.

33 de Maat *et al.* recently published their observations with iv paracetamol in adult medium and
34 intensive care [5]. The authors illustrated that iv paracetamol affects haemodynamics (i.e. induces
35 hypotension) in critically ill adults. They hereby confirmed other reports on the haemodynamic
36 (side)-effects of this drug in critically ill adults [6,7]. Since clinical characteristics, co-morbidity and
37 pharmacodynamics may be different in adults compared to neonates, we decided to quantify
38 haemodynamics following iv paracetamol in neonates, based on pooled data of observations
39 collected during a reported pharmacokinetic study [2] and an ongoing study on pharmacokinetics
40 and -dynamics of iv paracetamol (PARANEO, NCT 00969176).

41 Methods

42 Available cohorts

43 *Study 1: single dose pharmacokinetic study in neonates* [2]

44 Neonates admitted within 24 hours after birth and with an arterial line in place were included if
45 propacetamol (Prodafalgan®, Bristol Myers Squibb, Braine l'Alleud, Belgium) was administered.
46 Propacetamol is iv prodrug of paracetamol but necessitates plasma esterase activity. This esterase
47 function is already at adult level of activity in early life [4]. Propacetamol was administered when
48 neonates underwent minor, painful procedures (i.e. insertion of peripheral arterial or venous line,
49 insertion of central venous line, placement of chest tube) or as additional therapy in neonates on

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3 50 opioids. The decision to prescribe propacetamol or any other analgesic was made by the attending
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5 51 neonatologist. Exclusion criteria were major congenital malformations or severe birth asphyxia
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8 52 (Apgar < 4 at 5 minutes). In this study, 30 patients were included. In the first 15 patients, 20 mg
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10 53 (equal to 10 mg paracetamol)/kg was administered, in the next 15 patients, 40 mg (equal to 20 mg
11
12 54 paracetamol)/kg was administered. Mean birth weight was 2111 (SD 1094) g, mean gestational age
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14 55 (GA) was 33.8 (SD 3.9) weeks. Mean postnatal age at inclusion was 12.7 (SD 6.4) h. 10 neonates were
15
16 56 term, 20 were preterm (<37 weeks GA), of whom 10 <32 weeks GA [2].

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20 57 *Study 2: repeated dose PK/PD study (PARANEO, NCT 00969176, www.clinicaltrials.gov).*

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23 58 Interim analysis of a still ongoing study on pharmacokinetics, -dynamics and safety of repeated
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25 59 administration of iv paracetamol in the first 42 included neonates. Indications for initiation of
26
27 60 intravenous paracetamol were either medical or surgical painful conditions in line with guidelines of
28
29 61 the unit [8]. Mean weight was 2580 (SD 890) g, mean gestational age (GA) was 35.5 (SD 4.4) weeks.
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31 62 Mean postnatal age (days) was 3 (range 1-27) days, 22 neonates were term, 20 were preterm (<37
32
33 63 weeks GA), of whom 4 < 32 weeks GA. Primary outcome of this ongoing study are iv paracetamol
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35 64 pharmacokinetics in neonates, but pharmacodynamics - including haemodynamics - are also
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37 65 collected. The dosing regimen is based on a loading dose (20 mg/kg paracetamol), followed by an age
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39 66 dependent maintenance dose (5 to 10 mg/kg/6h) [3].
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45 2.Hemodynamics

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48 68 Individual patient files were analysed for data on blood pressure [mean, systolic, diastolic (mmHg)]
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50 69 and heart rate (beats/min) from just before the first administration of iv paracetamol until 6 hours
51
52 70 after initiation of iv paracetamol. We hereby focused on hemodynamic effects of the first dose.
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54 71 Besides absolute values (mmHg), any decrease in any mean arterial blood pressure < GA in mmHg for
55
56 72 a given GA (weeks, e.g. neonate of 30 weeks should have a mean arterial blood pressure of at least
57
58 73 30 mmHg) was recorded. This is the most frequently used, 'bedside' definition of clinical hypotension
59
60 74 in neonates [9]. All available observations are based on intra-arterial measurements.

75 3. analysis and statistics

76 For statistical analysis, Medcalc® (Mariakerke, Belgium) was used. From the individual data, mean
77 values and standard deviation were calculated when normal distribution was documented
78 (Kolmogorov-Smirnov test), otherwise reported by median and range.

79 Baseline values of haemodynamics were recorded just before initiation of iv paracetamol
80 administration. Correlations (spearman rank) between baseline values (heart rate, mean arterial
81 blood pressure) and clinical characteristics (weight, age) were investigated. Compared to baseline
82 haemodynamics, changes in parameters up to 6 h after iv paracetamol were collected. From the
83 individual data, mean values over the whole group were calculated. Paired Wilcoxon was
84 subsequently used to analyze changes compared to baseline (bpm, mmHg). One-way analysis of
85 variance (ANOVA) was used to test the difference between the means of the consecutive
86 measurements. Finally, incidence of hypotension was calculated, and characteristics of neonates who
87 developed hypotension (any time) following iv paracetamol were compared with normotensive cases
88 (Mann Withney-U).

101 Results

102 The pooled dataset consisted of haemodynamic observations in 72 neonates and both preterm
103 (n=40) and term (n=32) neonates were included. Baseline mean, systolic and diastolic blood pressure
104 before iv paracetamol were 46 (SD 7), 55 (SD 10) and 38 (7) mmHg while baseline heart rate was 145
105 (SD 20) bpm. Significant correlations between postmenstrual age and mean blood pressure ($r = -0.39$,
106 $p < 0.01$) or heart rate ($r = 0.28$, $p < 0.05$) were documented, reflecting the relative lower mean arterial
107 pressure and higher heart rate in the smallest neonates. Consecutive observations (mean, SD) on
108 heart rate and mean, systolic and diastolic blood pressure are provided in table 1.

109 There was a significant decrease (paired analysis) in heart rate 30 (-7 bpm), 60 (-4 bpm) and 120 (-8
110 bpm) (all at least $p < 0.05$) minutes following iv paracetamol with a subsequent trend towards
111 normalization but still remaining significantly lower (all $p < 0.05$) up to 360 minutes afterwards. Using
112 ANOVA, there were no significant differences in the consecutive measurements ($p = 0.36$). Mean
113 arterial blood pressure displayed a minor, statistically significant decrease (-3 mmHg) at 60 minutes,
114 with subsequent return to baseline values, without alterations in systolic or diastolic blood pressure.
115 Similarly, there were no significant differences in mean arterial pressures using ANOVA ($p = 0.75$).

116 Still 18 observations in 8 (9 %) neonates were below the threshold of normal mean arterial blood
117 pressure, defined as below the mmHg for the given gestational age/postmenstrual age at inclusion.
118 When clinical characteristics of hypotensive (n=8) were compared with normotensive (n=64) cases,
119 there was no significant difference in age (35 vs 36 weeks) or weight (2455 vs 2425 g), but baseline
120 mean arterial pressure (38 vs 47 mmHg, $p < 0.05$) was already lower in cases who subsequently
121 developed hypotension. Baseline heart rate was not significantly different (154 vs 142 bpm).

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3 125 **Discussion**
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6 126 Based on prospectively collected observations in 72 neonates, we observed a clinical very modest
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8 127 decrease in heart rate (-7 bpm) and mean arterial blood pressure (- 3 mmHg) following initiation of iv
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10 128 paracetamol. However, a minority of neonates (9 %) developed hypotension. Interestingly, these
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12 129 cases already had significantly lower blood pressures before administration of paracetamol.
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16 130 Effective management of pain should be based on systematic assessment of pain, followed by
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18 131 titrated administration of the most appropriated analgesic(s) with subsequent re-assessment. In any
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20 132 patient – also in neonates - the administration of an analgesic is a balanced decision based on
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22 133 perceived benefits (e.g. agitation, pain, stress) and risks (e.g. hypotension, bowel paresis,
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24 134 hypersensitivity, intolerance, withdrawal, neuro-apoptose) [10].
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29 135 When we focus on the haemodynamic impact of analgesics or sedatives in neonates, there are
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31 136 documented observations on effects of e.g. midazolam (+30 bpm, -3 mmHg)[11], fentanyl (-13 bpm, -
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33 137 3 mmHg) [12], fentanyl and midazolam (- 19 bpm, - 12 mmHg)[13], propofol (-9 bpm, -14 mmHg)[14]
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35 138 or morphine (-8 bpm, -3 mmHg)[15,16] on heart rate and mean arterial blood pressure. Pre-existing
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37 139 low mean arterial pressure was as risk factor for subsequent hypotension following morphine
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39 140 administration [16].
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44 141 Compared to the impact of other analgesics or sedatives in neonates, haemodynamic changes
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46 142 following iv paracetamol are limited, but not absent.
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55 145 Obviously, these changes following iv paracetamol at least in part likely represent improved
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57 146 analgesia, but it seems cautious to consider preadministration impaired haemodynamics as a relative
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59 147 contra-indication to initiate intravenous paracetamol.
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3 148 We can't but speculate why the extent of the impact of intravenous paracetamol on the
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5 149 haemodynamics seems to be different in neonates compared to the observations in adult intensive
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8 150 care setting. Hersch *et al.* [7] suggested that (traumatic) brain injury and pyrexia/hyperthermia are
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10 151 specific risk factors while de Maat *et al.* [5] were unable to unveil specific risk factors in their
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12 152 medium- and intensive care adult patients. At least, it was hereby reillustrated that focused studies
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15 153 on the pharmacokinetics and -dynamics of analgesics - including intravenous paracetamol - in early
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17 154 life are needed and feasible using appropriated methodology [1].
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Table 1

Haemodynamic effects of intravenous paracetamol administration in 72 (pre)term neonates. Heart rate and blood pressure (mean, systolic, diastolic) were reported by mean and standard deviation for all consecutive time intervals.

	Pre	30 min	60 min	120 min	180 min	240 min	300 min	360 min
Heart rate (bpm)	145 (20)	138 (21)	141 (20)	137 (20)	137 (22)	140 (20)	139 (20)	140 (21)
Blood pressure								
Mean (mmHg)	46 (7)	45 (7)	43 (8)	45 (8)	44 (7)	45 (8)	45 (8)	45 (8)
Systolic (mmHg)	55 (10)	52 (8)	51 (9)	53 (10)	51 (9)	53 (10)	51 (9)	52 (9)
Diastolic (mmHg)	38 (7)	39 (7)	38 (8)	39 (8)	38 (7)	39 (8)	37 (7)	39 (8)