Brief Report

Do Propylene Glycol, Benzyl Alcohol, and Ethanol in Concomitant Drugs Influence Clinical Outcomes Following Intravenous Acetaminophen in Critically Ill Neonates?

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Abstract: Propylene glycol (PG) and benzyl alcohol (BA) have been shown to inhibit the metabolizing enzyme for acetaminophen in the liver. Ethanol has unpredictable effects on acetaminophen metabolism. Critically ill neonates commonly receive drug formulations containing PG, BA, and ethanol as excipients. Until now, there have been no reports on the influence of BA, PG, and ethanol as excipients in patients undergoing concomitant acetaminophen therapy. We devised the present study to evaluate whether any significant differences in plasma acetaminophen concentrations, liver function tests, and serum creatinine exist between neonates receiving excipients containing drugs compared to those without. We included neonates that were administered intravenous acetaminophen with at least one concomitant drug containing either BA, PG, or ethanol as excipients. Plasma acetaminophen concentrations and levels of liver function were evaluated using tests. The doubling of alanine aminotransferase levels was considered to be a marker of hepatotoxicity. Elevation of serum creatinine >1.5 times higher than the baseline value was considered to be indicative of an acute kidney injury. Fifty-seven neonates were recruited in the study. No significant differences in the serum acetaminophen concentrations, liver and renal function tests, and rates of successful closure of ductus arteriosus were observed between the groups. No significant changes in the serum acetaminophen levels and the clinical outcomes were observed due to the presence of BA, PG, or ethanol in concomitant drugs as excipients. Probably, drugs containing these excipients can be safely administered, and even formulations containing these excipients with acetaminophen are likely to be safe for critically ill neonates.

Keywords: acetaminophen; paracetamol; excipient; propylene glycol; benzyl alcohol; ethanol

1. Introduction

Acetaminophen is a commonly administered drug in neonates as an antipyretic and analgesic, and it is recently used for the medical closure of hemodynamically significant patent ductus arteriosus. Although it is less common, hepatoxicity has been observed in neonates due to Cytochrome P450 2E1 (CYP2E1)-induced metabolites resulting in hepatocellular damage [1]. Toll-like receptor (TLR) and inflammasome activations were observed to contribute to acetaminophen-induced hepatotoxicity in pre-clinical studies [2]. Benzyl alcohol (BA) was shown to ameliorate the release of interleukins and caspase-1 cleavage by inhibiting TLR [2]. Another pre-clinical study observed that BA inhibited Cytochrome P450 enzyme production, and consequently, inhibited the metabolism of acetaminophen [3]. However, the authors of the same study have also observed that BA alone can cause mitochondrial membrane potential loss and cell toxicity at higher doses [3]. Similarly, propylene glycol (PG) has been observed to inhibit CYP2E1 in preclinical studies, and thus,

interfere with the production of hepatotoxic metabolite of acetaminophen [4]. Ethanol has unpredictable effects, as concomitant administration has been shown to competitively inhibit acetaminophen metabolism, while chronic administration can induce metabolizing enzymes in the liver [5,6].

Excipients are supposedly considered to be inactive elements in drug formulations. A pan-European study revealed that nearly a third of prescriptions for neonates contained at least one potentially harmful excipient [7]. We observed that certain drug formulations containing BA, PG, and ethanol are used in the neonatal population [8]. Commonly used excipients such as ethanol and propylene glycol tend to accumulate in neonates due to reduced elimination by the immature liver and kidneys [9,10]. Although the quantities of BA, PG, and ethanol that are administered are low when they are present as excipients, we are uncertain about their relative effects on neonates. Considering the potential impact of excipients in this vulnerable population, even the United States Food and Drug Administration has recently proposed changes in the antimicrobial syrup [11]. Until now, there have been no reports evaluating the interaction between BA, PG, and ethanol as excipients in drug formulations, which are concomitantly administered during acetaminophen therapy to critically ill neonates. Hence, we envisaged the present study as a preliminary attempt to evaluate serum acetaminophen concentrations and alterations in the liver and renal function tests when BA-, PG-, and ethanol-containing drug formulations are concomitantly administered to neonates who were administered intravenous acetaminophen therapy.

2. Results

2.1. Demographic Details

Fifty-seven neonates were recruited, and their demographic details are summarized in Table 1. Out of 57 neonates, 49 received acetaminophen for medical closure of PDA, and the remaining ones received it for analgesic/antipyretic purpose. All the neonates were admitted with the suspicion of sepsis and respiratory distress syndrome.

Table 1. Demographic characteristics of the study population.

| Variables		Overall (*n* = 57)	No Exposure to Excipients (*n* = 42)	Exposure to Excipients (*n* = 15)
Gestational age (weeks) $		28.7 (4.04)	29.1 (4.1)	26.8 (2.2)
Category of gestational age (*n*)	Term	4	4	0
	Late pre-term	4	3	1
	Very pre-term	18	16	2
	Extreme pre-term	31	19	12
Birthweight (kg) $		1.2 (0.8)	1.3 (0.8)	0.9 (0.4)
Category of birthweights (*n*)	Normal	4	4	0
	Low	6	5	1
	Very low	18	16	2
	Extremely low	29	17	12
Length (cm) $		35.2 (4.9)	36.1 (5)	33 (4.1)
APGAR #	1 min	6 (1–9)	7 (2–9)	6 (1–9)
	5 min	9 (5–10)	9 (6–10)	9 (5–10)
	10 min	10 (7–10)	10 (7–10)	10 (7–10)
Male:Female (*n*)		27:30	22:20	5:10
Duration of ICU stay (days) #		40 (3–121)	46 (8–121)	21.5 (3–91)

$ Represents mean (SD); # represents median (range).

2.2. Concomitant Drugs Containing BA, PG, or Ethanol

Fifteen neonates (26.3%) received concomitant drugs that contained one of the potentially interacting excipients evaluated in the present study. Hydrocortisone containing BA was administered to twelve neonates; phenobarbitone containing PG was administered to seven neonates; phenytoin containing PG and ethanol were administered to two neonates. Hydrocortisone and phenobarbitone (BA and PG) were concomitantly administered together to three neonates; phenytoin and hydrocortisone (BA, PG, and ethanol) were administered together to one neonate; hydrocortisone, phenobarbitone, and phenytoin (BA, PG, and ethanol) were administered together to one neonate.

2.3. Evaluation of Serum Acetaminophen Concentrations

Forty-nine neonates had at least one serum acetaminophen concentration that was recorded. Two-hundred and seventeen concentrations were recorded, which were estimated from the third dose to twenty-seventh dose. The median (range) acetaminophen concentration recorded in the study participants was 263 (7–748) µmol/L. The minimum and the maximum acetaminophen concentrations recorded between those that had at least one of BA-, PG-, or ethanol-containing concomitant drugs compared to those without potentially interacting concomitant excipients are depicted in Figure 1, and no significant differences ($p = 0.9$) were observed.
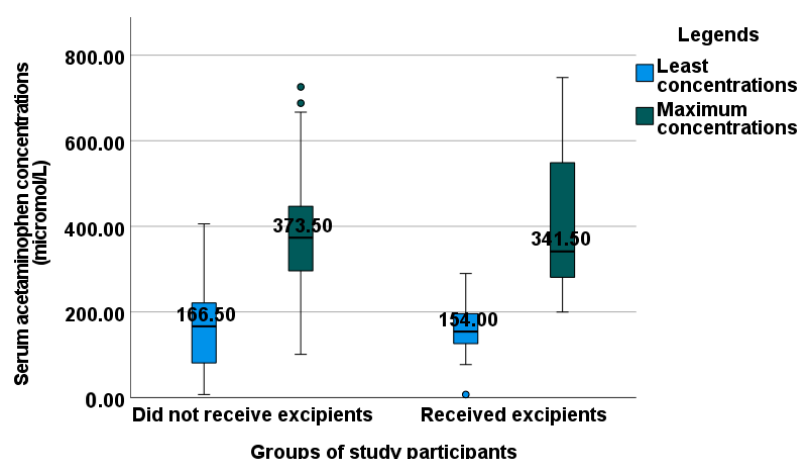
Figure 1. Comparison of serum acetaminophen concentrations between the groups.

The box plots represent the median and the ranges of the concentrations recorded in each study group.

Five (10.2%) neonates were observed with sub-therapeutic concentrations of acetaminophen, of which only one received a concomitant drug containing BA. Similarly, fourteen (31.8%) neonates received concomitant drugs containing one or more of BA, PG, or ethanol, but they had acetaminophen concentrations above the threshold level. No statistically significant differences ($p = 0.6$) were observed in the distributions of proportions of neonates with therapeutic acetaminophen concentrations between the groups.

2.4. Presence of Excipients and PDA Outcomes

Forty-nine neonates received acetaminophen for the medical closure of PDA, of which fifteen (30.6%) received concomitant drugs containing either BA, PG, or ethanol. Nine (60%) out of fifteen neonates had a successful closure, which was compared to 30/34 (88.2%), and this difference was not statistically significant ($p = 0.06$).

2.5. Liver and Renal Function Tests

The changes in the liver function tests and SCr were similar without any statistically significant differences ($p > 0.05$) observed in any of the parameters between the groups.

Six (10.5%) neonates were observed with ALT values that were twice as high during acetaminophen course, and none of these neonates received concomitant drugs containing BA, PG, or ethanol. Amongst the neonates receiving at least one of the potentially interacting excipients, none had signs of hepatotoxicity. No statistically significant difference ($p = 0.3$) was observed between the groups. None of the neonates met the criteria for AKI in both the groups.

3. Discussion

Benzyl alcohol, propylene glycol, and ethanol are generally regarded as safe (GRAS) when they are used in small quantities as excipients [12]. However, several recent reports have emerged attributing adverse events, such as lactic acidosis and osmotic dieresis, with these excipients [13]. Neonates are particularly vulnerable to toxic effects due to their immature liver enzymes and reduced renal elimination ability [14]. A recent randomized trial in adults with 4 g of acetaminophen per day with five milliliters of 99% propylene glycol for two weeks neither had any significant changes in the CYP-derived metabolites nor in the proportion of hepatotoxicity [15]. Ethanol and acetaminophen in combination resulted in the production of the glycolytic enzyme, glyceraldehyde-3-phosphate dehydrogenase, but not when either of them were administered alone [16]. Hence, most of the available evidence relating the acetaminophen and ethanol interaction emerged only from pre-clinical studies. In vitro studies revealed that acetaminophen inhibits the gastric- and first-pass metabolism of ethanol, resulting in toxicity, but this was observed only with toxic acetaminophen concentrations [17]. Concomitant acetaminophen and ethanol resulted in a higher degree of hepatocyte apoptosis compared to that of standalone agents [18]. Similarly, the simultaneous intake of ethanol and acetaminophen produces excess CYP2E1 metabolite, depleting glutathione, resulting in hepatotoxicity. However, a recent bioinformatics study revealed an absence of evidence with simultaneous acetaminophen and alcohol exposure [19]. A recent study also revealed that although CYP2E1 expression occurs in the fetal stage of life, it takes at least 90 postnatal days to reach adequate levels [20]. Hence, the interaction of acetaminophen with ethanol has been anecdotal and overtly exaggerated, and it has not been backed up by any sound scientific evidence [21]. In addition, neonates may be less susceptible to acetaminophen-induced hepatotoxicity due to the increased availability of glutathione, relatively larger size of the liver, and predominant sulfation pathway of metabolism [22]. This is also the reason why despite at high dose of 15 mg/kg/dose every six hours in preterm neonates, we did not observe any significantly higher rates of hepatotoxicity with acetaminophen. Similarly, BA through the activation of Toll-like receptor 4 has been shown to attenuate acetaminophen-induced hepatotoxicity in mice [23]. However, in the absence of clinical studies, we cannot be certain about the potential interactions between BA, PG, or ethanol with acetaminophen. We did not observe any significant interaction between the quantity of these excipients and acetaminophen.

The study is limited by the following: the small sample size; we did not evaluate the enzymatic expression; we did not evaluate the excipients in the oral acetaminophen formulations; we did not assess the metabolites.

4. Materials and Methods

4.1. Study Ethics and Design

This study was a prospective, observational study carried out between April 2018 and September 2020. We obtained approval from the Institutional Ethics Committee and consent from the parents. We adhered to the Declaration of Helsinki guidelines.

4.2. Study Procedure

Neonates that were administered intravenous acetaminophen (Perfalgan® at 15 mg/kg) for two or more days and those for whom we could record either or both serum acetaminophen concentration levels and liver function tests during therapy were included. Details on the following variables were collected: demographic details, concomitant drugs,

serum acetaminophen concentrations, liver function tests, and serum creatinine (SCr). Neonates were classified as pre-term (<37 weeks) and term neonates (≥37 weeks). The doubling of the amount of alanine amino transferase (ALT) with values exceeding the upper limit of normal reference range was considered as a marker of hepatotoxicity [24]. The following reference ranges were observed in the neonatal population: alkaline phosphatase (ALP) (IU/L): <250; alanine aminotransferase (ALT) (IU/L): <41; gamma-glutamyl transferase (GGT) (IU/L): <185; blood urea (mmol/L): 3.2–8.2; serum creatinine (mmol/L): 27–88. We defined an acute kidney injury (AKI) as SCr elevations >1.5 times the baseline value [25]. Preterm neonates were classified based on their gestational age as follows: extremely pre-term (<28 weeks); very pre-term (from 28 to <32 weeks); late pre-term (from 32 to <37 completed weeks of gestation) and term (>37 weeks) [26]. Birth weights were classified as follows: >2.5 kg—normal; from 1.5 to <2.5 kg—low; from 1 to <1.5 kg—very low; <1 kg—extremely low birth weights. We used the threshold steady-state (after third dose) therapeutic acetaminophen concentration of 60 μmol/L [27]. As a part of standard of care, serum acetaminophen concentrations were checked four hours after the third dose onwards, as per the treating physician's discretion. The details of estimation of serum acetaminophen concentrations have been mentioned previously [28].

4.3. Statistical Analysis

Descriptive statistics were used to represent the demographic characteristics. Numerical variables were tested for normal distribution, and accordingly, Mann–Whitney U test was used. Chi-square test for association with Yates correction was used for analysis of categorical variables. A *p*-value of <0.05 was considered to be significant. SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY, USA: IBM Corp.) was used for statistical analysis.

5. Conclusions

In conclusion, we did not observe any significant changes in the serum acetaminophen levels and the clinical outcomes due to the presence of BA, PG, or ethanol in concomitant drugs as excipients. Drugs containing these excipients can probably be safely administered, and even formulations containing these excipients with acetaminophen are likely to be safe for critically ill neonates.

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