The effects of palmvitee on δ-aminolevulinic acid-induced hyperbilirubinaemia in suckling rats

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Abstract

Introduction: Our previous study has shown that maternal administration of palmvitee reduced plasma total bilirubin in hyperbilirubinaemic rat neonates. Therefore, this study was conducted to investigate the effects of palmvitee on hyperbilirubinaemia induced by δ-aminolevulinic acid (ALA) in rat neonates.
Material and methods: Sixty Wistar rat neonates were divided into two groups. One group was injected 30 mg palmvitee/kg body weight intraperitoneally once daily starting on day 1 through day 14 postnatal, while the other group was given olive oil (control). At day 14 postnatal, half of the sucklings from each group were induced with hyperbilirubinaemia, while the rest were given vehicle. Twenty-four hours after the induction, the neonates were sacrificed. Plasma total bilirubin, hepatic thiobarbituric acid reactive substance (TBARS), UDP-glucuronyltransferase (UGT) activity and vitamin E content were determined.
Results: ALA administration increased plasma total bilirubin, but palmvitee pre-treatment prevented this increase (0.16 ±0.03 vs. 0.32 ±0.01 mg/dl). ALA administration did not affect the hepatic UGT activity, but in the neonates given palmvitee, it was reduced significantly. ALA also did not influence hepatic TBARS content. However, the TBARS was lower in the palmvitee-treated groups. The neonatal hepatic vitamin E content was increased following palmvitee pre-treatment.
Conclusions: Palmvitee administration confers protective effect against hyperbilirubinaemia. However, this administration could lead to a decreased hepatic glucuronidation activity in the hyperbilirubinaemic rat neonates induced by ALA.

Key words: tocotrienol, bilirubin, UDP-glucuronyltransferase, neonatal jaundice.

Introduction

Jaundice or hyperbilirubinaemia is a common phenomenon that occurs during the first days of postnatal life and it affects nearly two thirds of human newborns. It is often attributed to physiological immaturity of bilirubin metabolism, leading to excessive quantities of unbound bilirubin that can cross the blood brain barrier, damage the neuronal tissue and finally can increase the risk of neonatal death due to kernicterus [1]. Enhanced erythrocyte destruction rate contributes about 75% of bilirubin metabolism [2] in neonates and this leads to a higher production of bilirubin. The increased production of bilirubin exceeding its elimination activity, plays an important role in the mechanism of neonatal hyperbilirubinaemia [3]. The

major factor regulating the elimination of bilirubin is the rate of its glucuronidation in the liver which is catalyzed by UDP-glucuronyltransferase (UGT) [4]. Bilirubin is taken up by the liver and conjugated with glucuronides forming water-soluble and more easily excreted bilirubin [5]. Therefore, a low activity of UGT will increase the level of unconjugated bilirubin, which is lipid soluble and neurotoxic [3]. Rifampicin was reported to successfully treat unconjugated hyperbilirubinaemia in patients with Gilbert syndrome, a syndrome caused by a deficiency in UGT activity via the induction of its isoenzyme, UGT1A1 [6].

Phototherapy, an accepted modality for neonatal hyperbilirubinaemia management has been related to increased oxidative stress. In full term jaundiced neonates, plasma lipid peroxidation was elevated after the therapy [7, 8]. Therefore, the therapy can expose the infants to potent oxidative stress, and alternative treatment should be sought.

α-Tocopherol afforded a protective effect against hyperbilirubinaemia in a few studies. It decreased serum total bilirubin and the duration of phototherapy in the preterm [9] and full term babies [10]. The protective effect of the α-tocopherol could be due to its antioxidative property as well as its stabilizing effect on the erythrocytes [11]. Palmvitee, a vitamin E extract from palm oil, contains both tocopherol and tocotrienol. Similar to tocopherol, tocotrienol has also been shown to possess high antioxidative activity [12] and somewhat better than the former [13]. Abdul-Razzak *et al*. [14] had demonstrated that low level of plasma vitamins C and E were associated with significant hyperbilirubinaemia in full term neonates due to increased oxidative stress and intern red blood haemolysis. The red blood cells of preterm neonates were more prone to lipid peroxidation than that of the full term neonates [15].

Our previous study [16] has shown that maternal supplementation of the palmvitee throughout pregnancy reduced hyperbilirubinaemia in rat neonates. Therefore, in this study, we investigated the effects of the palmvitee administration in suckling rats on hyperbilirubinaemia.

Material and methods

Animals, reagents and diet

Fifteen-day pregnant female Wistar were supplied by the Laboratory Animal Resource Unit, Faculty of Medicine, Universiti Kebangsaan Malaysia. The pups born later were housed together with their littermates and individual mothers in polyethylene cages sized 45 × 28 × 20 cm during the course of the treatment. The dams were given free access to a commercial rat chow (Gold Coin Ltd., Malaysia) and water.

All chemicals and enzymes were of highest grade obtainable from Sigma-Aldrich (St. Louis, MO, USA), unless otherwise stated. The palmvitee used in this study was prepared by Malaysian Palm Oil Board according to Gapor *et al*. [17], comprising 21% α-tocopherol, 17% α-tocotrienol, 4% γ-tocopherol, 33% γ-tocotrienol and 24% δ-tocotrienol. Olive oil being the edible oil with the lowest content of vitamin E [18] was used as vehicle. The rat chow contained about 25.11 mg/kg total vitamin E and its composition is as follows (mg/kg food): α-tocopherol acetate 10.2, α-tocopherol 5.43, γ-tocopherol 0.8, α-tocotrienol 2.69, γ-tocotrienol 4.54 and δ-tocotrienol, 1.38.

Experimental design

Sixty suckling rats were divided into two groups. They were given 30 mg/kg body palmvitee intraperitoneally once daily or vehicle (control group) starting from day 1 postnatal for 14 days. At day 14 postnatal, each group was subdivided into another two groups; one group was administered δ-aminolevulinic acid (ALA, 500 µmol/kg body weight) intraperitoneally in three separate doses, 24, 20 and 16 h prior to sacrifice, following a procedure described by Drummond and Kappas [19] and another group was given an equivalent volume of normal saline. The final volume of each injection was 0.1 ml. The dose of the ALA and the age of the sucklings used in this study were based on our previous study [16]. Twenty-four hours after the first dose of ALA, the neonates were sacrificed. Neonatal blood via cardiac puncture and livers were taken under diethyl ether anesthesia. The plasma and livers were stored at –70°C until subsequent analyses. Pups with lysed blood were excluded because that would affect the bilirubin measurement.

The experimental procedure and animal handling in this study were approved by the Universiti Kebangsaan Malaysia Animal Care and Use and Medical Research Ethics Committee, which conforms to Malaysian Ministry of Science, Technology and Innovations guidelines.

Biochemical parameter measurements

Plasma total bilirubin was determined by means of a commercially available kit using an automated analyzer Cobas Mira S (Roche Diagnostic, Switzerland). The hepatic microsomes were prepared following a standard procedure [20] prior to the measurement of UDP-glucuronyltransferase (UGT) activity [21]. Malondialdehyde measured as thiobarbituric acid reactive substance (TBARS) content [22] and protein concentration [23] were determined in the livers of the neonates following the established methods. Hepatic vitamin E was extracted using the method of Podda *et al*. [24] with

some modifications [25] and analysed using an analytical high performance liquid chromatography (HPLC; Waters Corp., Milford MA, USA).

Statistical analysis

Results are expressed as mean ± standard error of mean. Data were statistically compared using one way analysis of variance (ANOVA), followed by Tukey's multiple comparison test using GraphPad Prism 2.1 software (1997; GraphPad Software Inc., San Diego, CA, USA). A p value < 0.05 was considered to indicate a significant difference between the groups.

Results

Effect of palmvitee on plasma total bilirubin

ALA administration increased plasma total bilirubin in rat neonates (Figure 1). Palmvitee pretreatment (30 mg/kg body weight) for 14 days, prevented the increase significantly ($p < 0.05$).

Effect of palmvitee on hepatic UGT

Figure 2 shows that ALA administration did not affect the activity of UDP-glucuronyltransferase (UGT) significantly in the control group. However, in the neonates given palmvitee, the enzyme activity in the ALA-treated group was significantly lower than the saline-treated group ($p < 0.05$).

Effect of palmvitee on hepatic lipid peroxidation

In Figure 3, the hepatic lipid peroxidation measured as thiobarbituric reactive acid substance (TBARS) was not affected by the ALA administration. Howver, in the palmvitee pretreatment groups, the hepatic TBARS content was reduced significantly ($p < 0.05$).

Effect of palmvitee administration on hepatic vitamin E content

Only α- and γ-tocopherols were detected in the livers of the rat neonates from the control group. ALA however, did not affect neonatal hepatic vitamin E content. Palmvitee pretreatment for 14 days increased all the tocopherol and tocotrienol isomers in the neonatal liver (Table I).

Discussion

In this study, as expected, δ-aminolevulinic acid (ALA) administration increased the plasma total bilirubin, and palmvitee pretreatment prevented the increase. This finding is in agreement with our previous study which showed that maternal administration of palmvitee reduced the parameter in the rat neonates [16]. α-Tocopherol has been shown to reduce plasma total bilirubin in preterm and term hyperbilirubinaemic newborns [9, 10]. It is believed that the low levels of the antioxidant

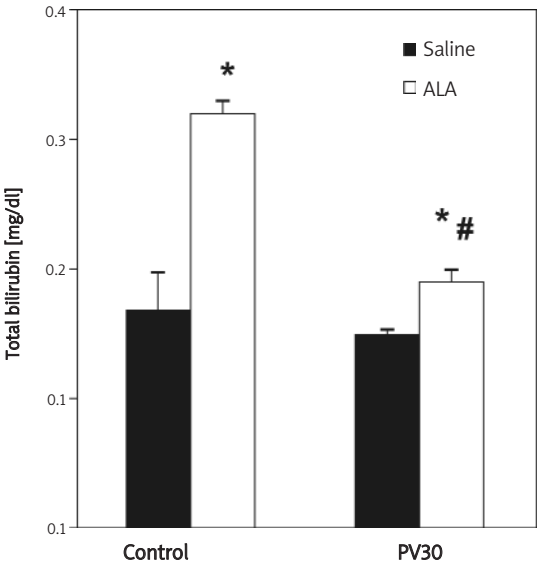

Figure 1. Plasma total bilirubin in suckling rats which were pretreated with intraperitoneal palmvitee (PV) at 30 mg/kg daily from day 1 through day 14 postnatal, after intraperitoneal administration of δ-aminolevulinic acid (ALA; 500 µmol/kg body weight) on day 14 postnatanal, in three divided doses 24, 20 and 16 h prior to acrifice (15 rats per group). Each bar represents mean ± standard error of mean **Significantly different from the saline groups (p < 0.05), #Significantly different from the control groups respectively (p < 0.05)*

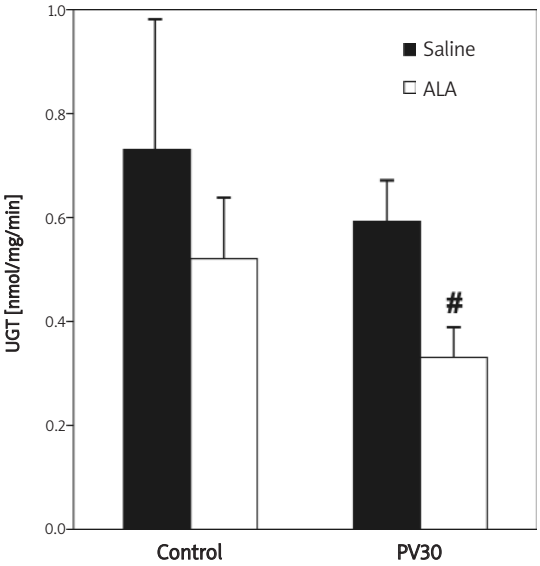

Figure 2. The effect of palmvitee (PV) pretreatment (30 mg/kg body weight) for 14 days (from day 1 through day 14 postnatal) on UDP-glucuronyltransferase (UGT) acitivity in δ-aminolevulinic acid (ALA)-treated suckling rats. The ALA (500 µmol/kg body weight) was administered at the end of pretreatment period in three divided doses 24, 20 and 16 h prior to sacrifice (15 rats per group). Each bar represents mean ± standard error of mean **Significantly different from the saline groups (p < 0.05)*

vitamins (C and E) may predispose them to increased oxidative stress and lead to hyperbilirubinaemia [14, 26].

ALA administration was used as a hyperbilirubinaemia model, by increasing haem synthesis and finally bilirubin production in animal models dose-dependently. The induction of hyperbilirubinaemia in rat neonates should be done between the age of 7 and 21 days due to inconsistencies in haem metabolism before the former age and maturation of hepatic glucuronidation after the latter age [19].

In our study, ALA administration did not affect the activity of UDP-glucuronyltransferase (UGT) in the control group. However, in the palmvitee-treated neonates, the significant reduction of the enzyme was observed in the ALA-treated group compared to the saline-treated group. In our previous study [16], the maternal administration of palmvitee at 50 and 200 mg/kg body weight decreased the hepatic UGT activity in the rat neonates. It is possibly that palmvitee competes with the bilirubin for the binding site in the enzyme, produces conformational changes that impede the binding of the substrate or depletes the hepatic UDP-glucuronic acid, the same hypotheses made on silymarin which was demonstrated to inhibit UGT1A1 [27, 28], the isoenzyme of UGT that metabolizes bilirubin. This isoenzyme is detectable from day 22 of gestation and gradually increases after birth in rats [29]. We could not explain why the inhibition of the enzyme was apparent in the palmvitee-treated group given ALA. These will need further investigation. However, we can suggest the use of phenobarbitone as a countermeasure should the palmvitee be used clinically in the treatment of neonatal jaundice and the reduction of UGT by the vitamin become apparent. Phenobarbitone is used clinically to treat neonatal jaundice [30] by inducing the UGT1A1 activity [31]. Nonetheless, the interaction that may occur between palmvitee and phenobarbitone requires another study.

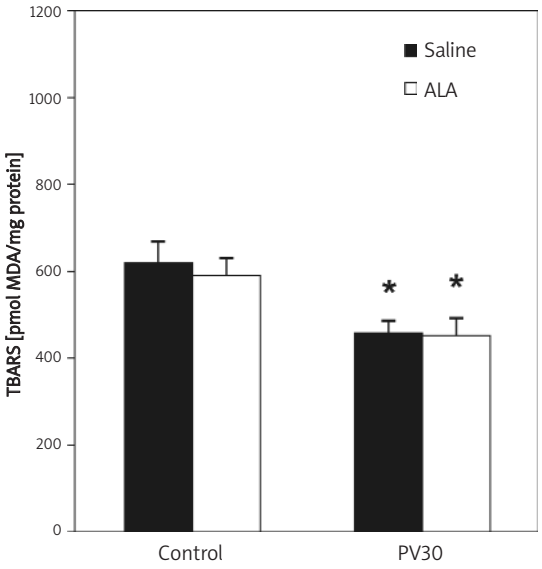

Figure 3. The hepatic TBARS (lipid peroxidation marker) content in rat neonates which were given 30 mg/kg body weight palmvitee (PV) pretreatment for 14 days starting from day 1 postnatal and given δ-aminolevulinic acid (ALA; 500 µmol/kg body weight) on day 14 postnatal, in three divided doses 24, 20 and 16 h prior to sacrifice (15 rats per group). Each bar represents mean ± standard error of mean
**Significantly different from the control groups respectively (p < 0.05)*

Diethyl ether anesthesia was reported to reduce bilirubin glucuronidation which finally affects the UGT activity [32]. In our preliminary study, we found that the anesthestic did not influence the UGT activity sgnificantly (data not shown), could be due to a shorter duration of exposure in our study i.e. less than a minute, than reported by Dills and Klaassen [32] (30 min to 4 h).

Our finding suggests that the decrease in plasma total bilirubin by palmvitee was not mediated by the increase in the hepatic bilirubin glucuronidation activity. α-Tocopherol was reported to decrease haem oxygenase activity, the rate-limiting enzyme in haem

Table I. Hepatic vitamin E (µg/g wet weight) content in palmvitee (PV)-pretreated suckling rats at 30 mg/kg body weight from day 1 of life for 14 days before administered δ-aminolevulinic acid (ALA) on day 14 postnatal

	Control		PV30	
	saline	ALA	saline	ALA
α-Tocopherol	6.91 ±0.49 (*91*)	6.43 ±0.41 (*93*)	10.73 ±1.13* (*25*)	11.17 ±1.16* (*27*)
α-Tocotrienol	0 (*0*)	0 (*0*)	6.91 ±1.17* (*16*)	6.54 ±1.43* (*16*)
γ-Tocopherol	0.63 ±0.06 (*9*)	0.51 ±0.05 (*7*)	2.32 ±0.37* (*5*)	2.16 ±0.44* (*5*)
γ-Tocotrienol	0 (*0*)	0 (*0*)	14.14 ±2.88* (*33*)	13.08 ±3.41* (*32*)
δ-Tocotrienol	0 (*0*)	0 (*0*)	8.79 ±1.71* (*21*)	8.40 ±2.01* (*20*)
Total	7.54 ±0.55	6.94 ±0.46	42.89 ±7.26*	41.35 ±8.45*

ALA was given in three divided doses 24, 20 and 16 h prior to sacrifice (500 µmol/kg body weight, 15 rats per group). Values are means ± standard error of mean. The italic numbers in parentheses indicate fractions (%) of the individual isomer detected from each group.
**Significantly different from the control groups respectively (p < 0.05)*

synthesis [33] which was found to be elevated after ALA administration [19, 34]. It could be that the palmvitee acts via the same mechanism. It is noteworthy to mention that this current study was a preliminary study. It will need further investigation regarding the effects of palmvitee on haem oxygenase and other enzymes involved in the bilirubin metabolism. On the other hand, Yin Zhi Huang, a traditional Chinese herbal medicine which has been used in neonatal jaundice treatment was shown to enhance bilirubin clearance and induce the expression of UGT [35].

Hepatic TBARS was not increased following ALA administration. However, the increase in hepatic lipid peroxidation was demonstrated following ALA administration at 40 mg/kg body weight for 10 days [36]. The dissimilarity could be due to the difference in ALA exposure. Plasma lipid peroxidation was also shown to be increase in babies with hyperbilirubinaemia compared to the healthy controls [7, 37]. Palmvitee pretreatment reduced this parameter significantly and this is afforded by its antioxidant property. In our previous study [16], ALA and maternal palmvitee pretreatment did not affect hepatic TBARS. The discrepancy could be due to the difference in dosage of palmvitee used and exposure timing. In the present study, 100% of the palmvitee administered received by the sucklings, but it was reported that in vitamin E placental transfer, only 20 to 30% those of the mother reached the fetus [38].

In the suckling rats pretreated with palmvitee, there was an increase in both hepatic tocopherol and tocotrienol contents, indicating that both types of vitamin E were taken up by the liver. ALA did not have any significant effect on the hepatic vitamin content. In the control groups, only tocopherol isomers were detected. More than 90% of the total vitamin E detected in the control groups was in the form of α-tocopherol, but in the groups given palmvitee, the hepatic vitamin E distribution were similar to the composition of the palmvitee used i.e. the highest being the γ-tocotrienol followed by α-tocopherol, δ-tocotrienol, α-tocotrienol and γ-tocopherol. In adult rats fed a combination of α-tocopherol and α-tocotrienol, the major isomer detected was α-tocopherol (more than 90%) [39]. A possible explanation could that α-tocopherol transfer protein, the protein which is responsible for biodiscriminational uptake of α-tocopherol into tissues [40] is poorly expressed in the neonatal rat liver. The activity of the protein results in high concentration of α-tocopherol in various tissues compared to the tocotrienols. However, in our previous study [16], in maternally palmvitee-pretreated neonates, the major vitamin E isomer detected was α-tocopherol, while δ-tocotrienol was not detected at all. The hepatic protein of α-tocopherol transfer protein expression was very low immediately after birth and only increased steadily during the two weeks of life before weaning [41], but it is mainly expressed in the mouse uteri [42].

In conclusion, the results obtained showed a promising therapeutic effect of palmvitee. The protective effect of the palmvitee in reducing plasma total bilirubin is possibly neither through its antioxidative mechanism nor by enhancing the activity of UGT. The exact mechanism of palmvitee would be pursued further. Its concomitant use with other drugs which undergo glucuronidation, also needs further investigations.

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