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Evaluation of efficacy of resin hemoperfusion in patients with acute 2,4-dinitrophenol poisoning by dynamic monitoring of plasma toxin concentration

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Abstract: Objective: The intoxications caused by 2,4-dinitrophenol (2,4-DNP), even death, have been frequently reported in recent years. This study aims to investigate the dynamic changes of plasma toxin concentration and explore the clinical value of resin hemoperfusion (HP) in the treatment of patients with acute 2,4-DNP poisoning. Methods: We reported 16 cases of acute 2,4-DNP poisoning through occupational exposure due to ignoring the risk of poisoning. The blood samples were collected from the 14 survivors. According to the different treatments of resin HP, the survivors were divided into routine HP (n=5) and intensive HP (n=9) groups. Ultra high performance liquid chromatography/tandem mass spectroscopy (UPLC-MS/MS) was used to detect the 2,4-DNP concentration in plasma in this study. Results: The 14 survivors recovered very well after treatment. The initial plasma 2,4-DNP concentrations (C_1) of survivors ranged from 0.25 to 41.88 μg/ml (mean (12.56±13.93) μg/ml). A positive correlation existed between initial plasma 2,4-DNP concentration (C_1) and temperature. The elimination of 2,4-DNP was slow and persistent, and the total clearance rates of plasma toxin from the 1st to 3rd day (R_3), the 3rd to 7th day (R_{3-7}), and the 1st to 7th day (R_7), were only (53.03±14.04)%, (55.25±10.50)%, and (78.29±10.22)%, respectively. The plasma toxin was cleared up to 25 d after poisoning in most of the patients. The R_3, R_{3-7}, and R_7 in the intensive HP group were all apparently higher than those in the routine HP group, with statistical significance (P<0.05). Simultaneously, the elimination half-life ($t_{1/2}$) of 2,4-DNP in the intensive HP group was apparently shorter than that in the routine HP group, with statistical significance (P<0.05). Conclusions: The clinicians should be aware of this slow and persistent process in the elimination of plasma 2,4-DNP. Higher initial plasma toxin concentration resulted in a more severe fever for the patient. According to the limited data, longer and more frequent resin HP may accelerate to eliminate the poison.

Key words: 2,4-Dinitrophenol, Poisoning, Hemoperfusion, Pharmacokinetics, Therapeutics
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1 Introduction

The 2,4-dinitrophenol (2,4-DNP) is an extensively used chemistry material in industry production, such as for insecticides, explosives, dyes, and wood preservatives (Miranda *et al.*, 2006; Colman, 2007; Lu *et al.*, 2011). The pharmacological properties of this chemical have long been known, including the causing of specific physiological and pathological changes. For example, 2,4-DNP had caused illness, even death, among French munitions workers at the end of the 1910s (Colman, 2007). Well into the 1930s, 2,4-DNP was once used as a famous prescription drug for weight loss, but was soon banned by the U.S. Food and Drug Administration, after the serious side effects, including death, were observed (Sebollela *et al.*, 2010). However, the intoxications caused by 2,4-DNP, even death, have often been reported in recent years (Daudu *et al.*, 2002; Suozzi *et al.*, 2005; Wang *et al.*, 2009; Grundlingh *et al.*, 2011; Jiang *et al.*, 2011;

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Phillips and Singer, 2013), primarily because some illegal drugs containing 2,4-DNP can proliferate through the Internet.

The current findings suggest that the main influential mechanism of 2,4-DNP is to uncouple the oxidative phosphorylation, so the energy from the aerobic metabolism can be released as heat instead of synthesizing adenosine triphosphate (ATP) (Colman, 2007). However, the detailed mechanisms need further research to confirm. For now, there is a big controversy on the effectiveness and side effects of dantrolene for 2,4-DNP therapy, so supportive managements are the best treatment option until now (Grundlingh *et al.*, 2011). In general, oral ingestion is the most common way for 2,4-DNP poisoning (Daudu *et al.*, 2002; Suozzi *et al.*, 2005; Wang *et al.*, 2009; Grundlingh *et al.*, 2011; Phillips and Singer, 2013).

All the patients in this report were poisoned by non-oral exposure. Although the clinical features and treatments have been reported (Lu *et al.*, 2011), this study is to analyze the dynamic changes of plasma toxin concentration and explore the clinical value of resin hemoperfusion (HP) in the treatment of patients with acute 2,4-DNP poisoning.

2 Materials and methods

2.1 Ethics statement

This research was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University (Hangzhou, China). Because these patients were all admitted in an urgent need situation, and the detection of plasma toxin concentration was necessary to the diagnosis and treatment, and as no extra costs or procedures would be generated, the permission to use of patients' plasma toxin concentration data in this study was obtained by verbal informed consent from all the patients or their next of kin, and all the data were analyzed anonymously. The ethics committee specifically approved such a procedure.

2.2 Clinical data

Detailed information regarding the 16 patients (2 victims and 14 survivors) had been reported in our previous studies (Lu *et al.*, 2011). Patients (12 males and 4 females) were all relatives working in a family factory, and were poisoned by coming in contact with 2,4-DNP through a non-oral approach. Two of the patients died of cardiac arrest within 3 h after admission. The remaining 14 patients accepted supportive treatments involving HP, which was administered to the patients within 6 h after admission. Styrene/divinylbenzene copolymer (HA330 macroporous resin, Zhuhai Lizhu Biomedical Materials Co., Guangdong, China) was used for HP treatment. Due to the deficiency of previous experience, we adjusted the therapeutic schedule of resin HP according to the clinical condition evolution and plasma toxin concentration of the patients. Five cases with mild symptoms were treated with routine HP in one HP apparatus lasting 4 h once a day for 3 consecutive days. These 5 patients exhibited lower plasma toxin levels and were enrolled in the routine HP group. The rest of the 9 cases with severe symptoms were treated with intensive HP in two HP apparatuses lasting 6–8 h once a day for the first 3 d, and then routine HP for the later 3 d. These 9 patients had higher plasma toxin levels and were considered as the intensive HP group. The remaining 14 patients recovered very well, and no evident poisoning sequelae were found during the 3-year follow-up.

2.3 Dynamic detection of plasma toxin concentration

The blood samples of the remaining 14 patients were collected on the 1st (on admission, before HP), 2nd (after HP), 3rd (after HP), 5th, 7th, 9th, and 25th days after poisoning. An ultra high performance liquid chromatography/tandem mass spectroscopy (UPLC-MS/MS) (Waters, Milford, Massachusetts, USA) was used to detect the plasma 2,4-DNP concentration (Politi *et al.*, 2007; Sebollela *et al.*, 2010; Dejmkova *et al.*, 2011; Liu *et al.*, 2011; Wang *et al.*, 2014).

To extract 2,4-DNP, a 1-ml sample of whole blood was transferred into an Eppendorf tube, which was centrifuged at 3500*g* for 5 min. A 200-μl sample of the supernatant was mixed with 400 μl acetonitrile to precipitate protein. After the mixture was vortexed and centrifuged at 3500*g* for 5 min, 400 μl of the supernatant was mixed with a 500-μl mobile phase (10 mmol/L formic ammonium plus acetonitrile, 9:1 (v/v)), filtered through a membrane, and analyzed

using UPLC-MS/MS. The limit of quantitation for plasma 2,4-DNP concentration was 0.01 μg/ml.

2.4 Total clearance rate of plasma toxin

The total clearance rates were calculated according to the following formulas: $R_3=(C_1-C_3)/C_1\times 100\%$, $R_{3-7}=(C_3-C_7)/C_3\times 100\%$, and $R_7=(C_1-C_7)/C_1\times 100\%$, representing the total clearance rates of plasma toxin from the 1st to 3rd day, the 3rd to 7th day, and the 1st to 7th day, respectively. C_1 stood for the plasma toxin concentration at the time (1st day) of hospital admission before HP, while C_3 and C_7 represented the plasma toxin concentrations at the 3rd and 7th day, respectively. And C_3 represented the plasma toxin concentration after HP.

2.5 Elimination half-life of plasma toxin

A one-compartment model with linear first-order elimination was used to describe the plasma concentration versus time data. The elimination rate constant (k) for 2,4-DNP from the 1st to 7th day was empirically determined from $k=(\ln C_1-\ln C_7)/(t_7-t_1)$, where t_1 and t_7 represented the point-in-time at the 1st and 7th day, respectively. Subsequently, the elimination half-life ($t_{1/2}$) of 2,4-DNP was calculated by $t_{1/2}=0.693/k$.

2.6 Statistical analysis

Data were analyzed using an SPSS 13.0 software package (SPSS Inc., Chicago, IL, USA). The one-sample Kolmogorov-Smirnov test was used to evaluate the normality of their distribution. Parametric data like age, oral temperature, plasma toxin concentration, and the total clearance rate followed normal distribution and were represented as mean±standard deviation (SD). These variables in the two groups were compared using the independent t-test. The Fisher's exact test was used for the comparison of gender distribution between the two groups. The relationship between the initial plasma toxin concentration (C_1) and oral temperature was evaluated using the Pearson product-moment correlation. To explore the role of resin HP in treatment of patients with acute 2,4-DNP poisoning, the total clearance rates of three different periods (R_3, R_{3-7}, and R_7) between the routine HP and intensive HP groups were also compared by the independent t-test. Statistical significance was set at a P-value of less than 0.05.

3 Results

3.1 Patients' characteristics

Fourteen patients with 2,4-DNP poisoning were prospectively included with an average age of (36.3±17.1) years (range 16–64 years). There were 3 females and 11 males in the cohort of patients. During the treatment, no obvious dysfunctions of the liver and kidney occurred in the 14 survivors.

The patients' characteristics within two groups are shown in Table 1. The gender and age were similar between the two groups. The initial oral temperature and plasma toxin concentration (C_1) were significantly higher in the intensive HP group than in the routine HP group (all $P<0.05$).

3.2 Relationship between initial plasma toxin concentration and temperature

By using the Pearson product-moment correlation, we found a positive correlation between initial plasma 2,4-DNP concentration (C_1) and oral temperature in 14 patients ($r_s=0.878$, $P<0.05$; Fig. 1). It revealed that higher initial plasma toxin levels resulted in higher temperatures in the patients.

3.3 Dynamic changes of plasma toxin concentration of 14 survivors

In this study, all survivors were hospitalized and monitored up to 25 d after poisoning. The initial plasma 2,4-DNP concentrations (C_1) of survivors ranged

Table 1 Patients' characteristics in this study

HP group	Age (year)	Gender M/F	Initial oral temperature (°C)	Initial plasma toxin concentration C_1 (μg/ml)	HP times/No. of HP apparatus	
					1st to 3rd day	3rd to 7th day
Routine (n=5)	31.0±19.8	3/2	37.7±0.3	0.51±0.24	3/3	0/0
Intensive (n=9)	39.2±15.8	8/1	38.7±0.8	19.26±8.08	3/6	3/3
P-value	0.409	0.505	0.015	0.009		

from 0.25 to 41.88 μg/ml (mean (12.56±13.93) μg/ml), and were greater than 15.0 μg/ml in 6 cases. Dynamic changes of plasma toxin concentration in the 14 patients from the 1st to 7th day are shown in Fig. 2. The plasma 2,4-DNP concentration of 14 survivors declined about (53.03±14.04)% after the first 3 d (R_3). The total clearance rate of plasma toxin from the 3rd to 7th day (R_{3-7}) was (55.25±10.50)%, and from the 1st to 7th day (R_7) was (78.29±10.22)%. Furthermore, residual plasma toxin could be detected in 7 patients after 9 d and in 3 patients after 25 d. The plasma 2,4-DNP concentrations of all survivors were all below 6.0 μg/ml after 9 d.

3.4 Comparison of total clearance rates between routine and intensive HP groups

Among the survivors, 5 cases were enrolled in the routine HP group, and their R_3, R_{3-7}, and R_7 were (39.72±5.29)%, (47.04±6.84)%, and (67.85±6.27)%, respectively. The rest of the 9 cases were in the intensive HP group, and their R_3, R_{3-7}, and R_7 were (60.43±11.59)%, (59.81±9.50)%, and (84.09±6.63)%, respectively. The R_3, R_{3-7}, and R_7 in the intensive HP group were all apparently higher than those in the routine HP group, with statistical significance (all $P<0.05$; Fig. 3).

3.5 Comparison of elimination half-life between routine and intensive HP groups

The elimination half-life ($t_{1/2}$) of 2,4-DNP was (88.78±14.66) h in the routine HP group, while the $t_{1/2}$ was only (54.58±12.92) h in the intensive HP group. The $t_{1/2}$ of 2,4-DNP in the intensive HP group was apparently shorter than that in the routine HP group, with statistical significance (t=4.535, P=0.001).

4 Discussion

Theoretically, 2,4-DNP is absorbed through the acidic stomach and can passively permeate cell membranes through water channels regardless of their ionization state. Furthermore, it can enter the human body through gastrointestinal, respiratory, and epidermal routes (Colman, 2007; Fongmoon *et al.*, 2014). The absorption rate of 2,4-DNP through the skin is much slower than that by other routes because of low partition coefficients. However, all the patients in this study were most likely poisoned primarily through skin contamination.

After absorption, it rapidly distributes to the liver, lungs, and kidneys without being stored in or bound by tissues. The highest concentration of 2,4-DNP was detected in plasma (Grundlingh *et al.*, 2011). The present study showed obviously higher initial plasma

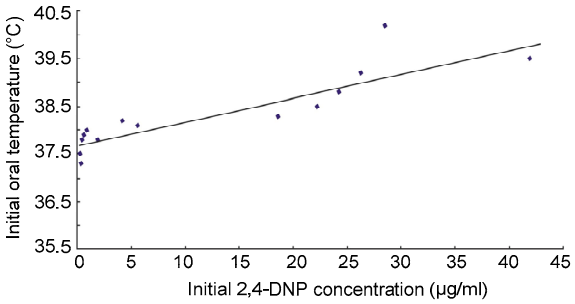

Fig. 1 Distribution and correlation of initial 2,4-DNP concentration (C_1) and oral temperature of patients on admission

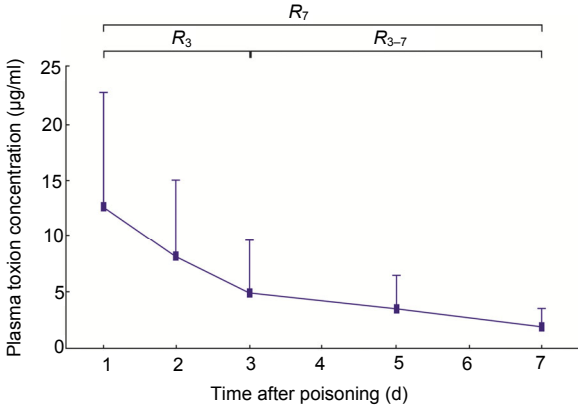

Fig. 2 Dynamic changes of plasma 2,4-DNP concentrations in 14 patients from the 1st to 7th day
Data are expressed as mean+SD (n=14)

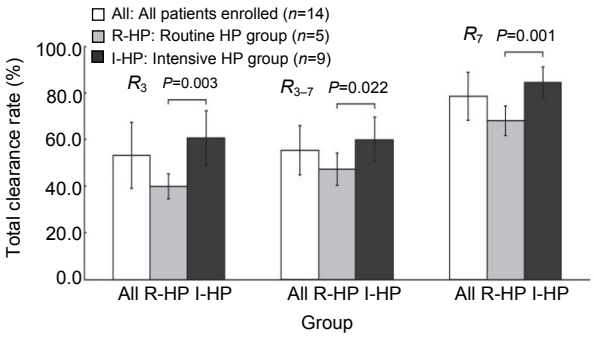

Fig. 3 Comparison of total clearance rates in different periods between routine and intensive HP groups
Data are expressed as mean±SD

2,4-DNP concentration in higher temperatures of patients, which may reflect the severity of poisoning. Less toxic metabolites, such as 2-amino-4-nitrophenol and 4-amino-2-nitrophenol, may be generated from 2,4-DNP, and some may be conjugated to glucuronic acid or sulfate. The major route of 2,4-DNP metabolism is through the liver, and most metabolites are excreted in the urine together with prototypical 2,4-DNP. Data for the pharmacokinetics of 2,4-DNP in animal models vary greatly (Szczepańska-Sadowska, 1975; Phillips and Singer, 2013). There are no reliable data to define the pharmacokinetics of 2,4-DNP in humans. In the studies of Robert and Hagardorn (1983; 1985), 2,4-DNP was detected 96 h after a single gavage dose of 22.5 mg/kg in mice. In our study, the elimination of 2,4-DNP was slow and persistent, and the total clearance rates of plasma toxin after 3 (R_3) and 7 (R_7) d were only (53.03±14.04)% and (78.29±10.22)%, respectively. The plasma toxin was cleared up to 25 d after poisoning in most of the patients. Higher initial plasma concentration of 2,4-DNP resulted in the duration of plasma toxin for a longer period of time. In this study, the first purpose was to remind the clinicians being aware of the slow and persistent process of the elimination of plasma toxin in this type of poisoning case.

Considering its lipid solubility, 2,4-DNP should readily distribute to and store in fat tissue, which can result in "secondary poisoning". However, presently no relevant data are available. Controversy still surrounds the efficiency of HP for removing 2,4-DNP. Theoretically, the styrene/divinylbenzene copolymer (resin) used in HP should effectively absorb lipophilic compounds. Without pharmacokinetic data from well-controlled studies, we cannot make firm conclusions regarding the scavenging action of resin HP. Certainly, it can simultaneously maintain electrolyte balance, control body temperature, and protect the liver and kidney. Moreover, resin HP has successfully treated some patients who have overdosed on highly lipid solubility drugs (Licari *et al.*, 2009; Sikma *et al.*, 2012; Zhang *et al.*, 2012; Brandenburg *et al.*, 2014; Shang and Lu, 2015). Such poisoning accidents were rare and are clinically critical, and it was difficult to perform a well-controlled study. Clinically, since the condition of a patient with acute 2,4-DNP intoxication is closely related to the plasma toxin concentration, the therapeutic effect of HP is closely associated with the elimination efficiency of HP on plasma toxin. In our study, the total clearance rate in the intensive HP group was apparently higher than that in the routine HP group, with statistical significance. Simultaneously, the elimination half-life ($t_{1/2}$) of 2,4-DNP in the intensive HP group was apparently shorter than that in the routine HP group, with statistical significance. It inferred that the different time and intensity of resin HP might be the reason to the differences in the total clearance rate and elimination half-life ($t_{1/2}$) between the two groups. In view of the therapeutic process of these patients, we tend to think that longer and more frequent resin HP may accelerate the elimination of the poison.

This clinical study has several limitations. First, the plasma 2,4-DNP concentration before HP treatment in the two groups varied significantly, and might influence the elimination effect of resin HP on plasma toxin. Second, the sample size was not large and the randomization was not implemented nicely, based on a cohort study. Third, due to the limited conditions, the dynamic monitoring of plasma 2,4-DNP concentration was not implemented in the process of resin HP, which might be more accurate in evaluating the scavenging effect of resin HP. Fourth, all the cases came from one family in this study, slightly lacking in representation. Thus, further clinical or animal studies are needed to find out the optimized therapeutic time and frequency of resin HP for patients with acute 2,4-DNP poisoning so as to improve their overall prognosis.

Compliance with ethics guidelines

Xue-hong ZHAO, Jiu-kun JIANG, and Yuan-qiang LU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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中文概要

题　目：血液灌流对急性 2,4-二硝基苯酚中毒患者的毒物清除疗效评估

目　的：本研究通过监测急性 2,4-二硝基苯酚中毒患者治疗前后血浆毒物浓度的动态变化，从而探讨血液灌流治疗对急性 2,4-二硝基苯酚中毒患者的毒物清除疗效及其临床价值。

创新点：由于急性 2,4-二硝基苯酚中毒患者在临床中较为罕见，其相关毒物代谢动力学资料十分缺乏，且尚未有规范的临床救治方案。本研究创新点主要有：（1）对 2,4-二硝基苯酚的毒物代谢动力学进行了必需的探讨和研究；（2）为临床上形成规范的救治方案，提供了科学的实践资料。

方　法：回顾性分析了 16 例急性 2,4-二硝基苯酚中毒患者的救治经过，其中 14 例幸存者根据救治中实施

树脂-血液灌流治疗的强度和频度差异，分为常规血液灌流组（5 例）和强化血液灌流组（9 例）。同时，本研究使用超高效液相色谱串联质谱方法对患者救治过程中的血浆毒物浓度进行了动态监测。

结　论：14 例幸存患者的初始血浆 2,4-二硝基苯酚浓度为 0.25~41.88 μg/ml 不等，且初始血浆毒物浓度与患者体温高低呈正相关。研究发现，机体对于 2,4-二硝基苯酚的清除是缓慢而持久的。根据血浆 2,4-二硝基苯酚浓度动态变化计算而得，患者血浆毒物总清除率 R_3（中毒后第 1 日至第 3 日）、$R_{3–7}$（中毒后第 3 日至第 7 日）和 R_7（中毒后第 1 日至第 7 日）分别为 (53.03±14.04)%、(55.25±10.50)% 和 (78.29±10.22)%。其中，强化血液灌流组患者的血浆毒物总清除率 R_3、$R_{3–7}$ 和 R_7 均显著高于常规血液灌流组，差异有统计学意义（P<0.05）。此外，强化血液灌流组患者的 2,4-二硝基苯酚清除半衰期（$t_{1/2}$）明显短于常规血液灌流组，差异有统计学意义（P<0.05）。因而，本研究显示高强度、高频度地实施血液灌流治疗有利于急性 2,4-二硝基苯酚中毒患者清除毒物。

关键词：2,4-二硝基苯酚；中毒；血液灌流；药代动力学；治疗学