行政院國家科學委員會專題研究計畫　成果報告

靜脈氧化砷治療之心臟毒性研究：發生率、機轉及發生後之可逆性

計畫類別：個別型計畫
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計畫主持人：吳美環

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一、中文摘要

靜脈三氧化砷治療對於急性骨髓前白血病療效良好，但臨床經驗顯示有可能有心臟毒性。本研究以分離兔心臟灌流之實驗模式，探討是否三氧化砷有直接之心臟毒性，包括其發生率、電生理特性之變化與不整脈之誘發狀況。

我們發現，三氧化砷於臨床治療濃度（1，3，10μM）或更高（30μM）之濃度，並不會影響心電生理特性，但若以極高之濃度（300μM）（此種濃度只有可能在中毒下遇到）則 QT 間距會延長。此外，我們另設立長期靜脈三氧化砷治療之動物模式，實驗兔接受每天 0.2mg/kg 之靜脈三氧化砷，30 天後再行測定。我們發現，接受長期靜脈三氧化砷治療之實驗，其 QT 間距延長顯著變長，且會誘發心室頻脈（1/7，14%），組織濃度之檢定亦顯示砷堆積之現象。但此種砷堆積之現象有可能於停藥後，部分會再度排出。

關鍵詞：三氧化砷、心臟電生理學、不整脈

Abstract

Although parenteral administration of As_2O_3 is highly effective in the treatment of acute promyelocytic leukemia, cardiac toxicity has been reported. This study employed Langendorff- perfusion to determine the direct effects of As_2O_3 in the electrophysiological properties of rabbit hearts after acute or chronic As_2O_3 treatment (0.2 mg/Kg/day intravenous for 30 days). Tissue accumulations of arsenicals, pathological changes as well as the reversibility of chronic As_2O_3 effects were assessed. We found that cardiac conduction and repolarization were not altered whatsoever after acute As_2O_3 treatment at clinically relevant (1, 3, 10 μM) and higher (30 μM) doses. Nevertheless, an extremely high concentration of As_2O_3 (300 μM) prolonged the corrected QT interval. Subsequent to chronic As_2O_3 administration and with 30 μM As_2O_3 via Langendorff perfusion, polymorphic ventricular tachycardia was observed (1/7, 14%). Corrected QT interval was prolonged, while basic cycle length was shortened. Significant accumulation of arsenicals in the cardiac tissue was found, but without any pathological changes. After As_2O_3 was discontinued for 30 days, the chronic As_2O_3 -induced electrophysiological changes improved, no ventricular arrhythmia was noted, and the tissue concentration of arsenicals decreased considerably. We therefore conclude that although no immediate cardiac effects were discernable at clinically relevant doses, an extremely high concentration of As_2O_3 could prolong ventricular repolarization. Chronic As_2O_3 treatment resulted in a prolonged ventricular repolarization, in association with arsenicals accumulation and with risk of ventricular tachycardia. These chronic cardiac toxicities and the tissue accumulation of arsenicals were, however, partially reversible after cessation of As_2O_3.

Keywords: arsenic trioxide, heart, electrophysiology

二、緣由與目的

Arsenic trioxide (As_2O_3) may induce complete remission in patients with relapsed or refractory acute promyelocytic leukemia (Shen et al., 1997; Soignet et al., 1998; 2001). However, clinical trials have demonstrated cardiac adverse events resulting from As_2O_3 therapy, including QT interval prolongation, complete atrioventricular block, premature ventricular contractions, ventricular tachycardia, and a potentially fatal torsade de pointes ventricular arrhythmia (Huang, et al. 1998; Huang et al. 1998; Ohnish et al., 2000; Unnikrishnan et al., 2001). Because reported cases of these events usually occurred in association with previous anthracycline therapy, electrolyte disturbances or other systemic problems, the direct cause-effect relation between As_2O_3 treatment and these cardiac adverse events remains uncertain. In a recent study, As_2O_3 was shown to prolong the action potential duration in isolated guinea-pig papillary muscle with a slow pacing cycle length (Chiang et al. 2001). Nonetheless, the modification of cardiac electrophysiological profile and the proarrhythmic potential after As_2O_3 are still undefined.

The part I study was to define the direct effects of As_2O_3 after acute and chronic parenteral administration of As_2O_3 by using the intracardiac recording and stimulation in isolated hearts in Langendorff perfusion.

三、結果與討論

RESULTS

Acute As_2O_3 treatment

The acute effects of As_2O_3 at concentrations including 1, 3, 10 and 30 μ M were assessed in 8 rabbits and at extremely high concentrations (30, 100 and 300 μ M) in another three rabbits. Previous study had indicated that the mean peak plasma arsenic level was 6.9 μ M (ranged 5.5 to 7.3 μ M) in patients with acute promyelocytic leukemia receiving 10 mg daily As_2O_3 (Shen et al., 1997). Therefore, concentrations used in this experiment may be representative of clinically relevant (1, 3 and 10 μ M), even 5 times higher (30 μ M), or only encountered accidentally concentrations (100 and 300 μ M). Intracardiac recording was used to detect the atrial activities, His potential, ventricular activities and repolarization (T wave). Changes with regard to the electrophysiological parameters after acute treatment of As_2O_3 at concentrations of 1, 3, 10 and 30 μ M in the 8 rabbits are summarized in Table 1. We found that the electrophysiological parameters were not significantly altered after As_2O_3 treatment. The spontaneous cycle length, repolarization (QT interval and QT interval corrected according to the Bazett formula), refractoriness and the conduction velocity over the cardiac tissues were not significantly changed. No arrhythmias were observed during the experiments.

After the treatment with an extremely high dose of As_2O_3 (30, 100 and 300 μ M) that may be encountered accidentally, most of the cardiac electrophysiological parameters were not significantly altered. Only the corrected QT interval was lengthened by extremely high concentration of As_2O_3 (300 μ M) (from 362 ±19 to 414 ±23 ms, p = 0.02)

Chronic As_2O_3 treatment

Chronic As_2O_3 effects were assessed in 7 rabbits that were killed after having received daily parenteral administration of As_2O_3 for 30 days.

Cardiac electrophysiological modification

After chronic parenteral administration of As_2O_3, polymorphic ventricular tachycardia occurred in one out of 7 rabbit hearts (14%). The corrected QT interval was significantly lengthened and the spontaneous cycle length was shortened. However, the conduction through the atrial, atrioventricular tissue and the His-Purkinje system was not slowed down. The refractoriness of the cardiac tissues, including the atrial, atrioventricular, His-Purkinje system and ventricular tissues, was also not altered.

Tissue distribution of arsenicals after

chronic As_2O_3 treatment

The distribution of arsenicals in various organs of the 5 rabbits killed after chronic parenteral As_2O_3 treatment is summarized in Table 3. Significant tissue accumulation was observed in liver, bladder, heart, lung and kidney. The concentration of arsenicals in cardiac tissue was comparable to that of bladder and higher than that of lung.

DISCUSSION

As_2O_3 therapy is highly effective for the induction of remission in adults or children with promyelocytic leukemia (Shen et al., 1997, Soignet et al., 1998, 2001). However, adverse cardiac events, including QT prolongation, atrioventricular block or torsade de pointes ventricular tachycardia have been reported in clinical trials of As_2O_3 (Soignet et al., 2001, Huang et al., 1998; Huang et al., 1999; Ohnish et al., 2000; Unnikrishnan et al., 2001). The mechanisms responsible for these events are still unclear. This study observed the following results: 1) Acute As_2O_3 treatment at clinically relevant or 5 times higher doses did not modify the cardiac electrophysiological properties, but acute As_2O_3 treatment at clinically 50 times higher dose prolonged the cardiac repolarization; 2) After chronic As_2O_3 parenteral administration, clinically 5 times higher dose of As_2O_3 could lengthen the repolarization of cardiac tissue and was associated with increased risk of ventricular tachycardia; 3) After chronic As_2O_3 parenteral administration, tissue accumulation of arsenicals occurred and may have accounted for the emergence of cardiac toxicities in the chronic phase of As_2O_3 therapy; and 4) The electrophysiological effects and tissue accumulation of arsenicals after chronic As_2O_3 parenteral administration were partially reversible after cessation of As_2O_3 administration.

In conclusion, this study found that cardiac toxicity could be induced by chronic parenteral administration As_2O_3 in rabbits. Acute As_2O_3 treatment at clinically relevant or 5 times higher concentrations did not significantly alter cardiac electrophysiological properties in our animal model. At only extremely high concentration, acute As_2O_3 administration could prolong the corrected QT interval (ventricular repolarization). However, only after chronic parenteral administration, probably related to arsenicals accumulation in the cardiac tissue, were the corrected QT interval prolonged and the risk of ventricular arrhythmias increased by As_2O_3 at a dose that was not associated with acute cardiac toxicity. The possible development of these direct cardiac toxicities should be closely monitored during the chronic phase of As_2O_3 therapy. However, these chronic cardiac toxicities and tissue accumulation of arsenicals by As_2O_3 therapy were at least partially reversible after cessation of As_2O_3 administration

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附件一

行政院國家科學委員會補助專題研究計畫 □ 成 果 報 告 □期中進度報告

靜脈氧化砷治療之心臟毒性研究：發生率、機轉及發生後之可逆性

計畫類別：□ 個別型計畫　　□ 整合型計畫
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主持人：吳美環　教授 台大醫學院小兒科
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共同主持人：林君榮 助理教授　台大醫學院
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成果報告類型(依經費核定清單規定繳交)：□精簡報告　□完整報告

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□國際合作研究計畫國外研究報告書一份

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