Tissue distribution of arsenic species in rabbits after single and multiple parenteral administration of arsenic trioxide: tissue accumulation and the reversibility after washout are tissue-selective

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摘要

Abstract

Parenteral administration of arsenic trioxide has recently been recognized as an effective antineoplastic therapy, especially for the treatment of acute promyelocytic leukemia . Its efficacy and toxicity are concentration-dependent and are related to the fractions of different arsenic species and the degree of methylation. In this study, arsenic trioxide was given parenterally to rabbits as a single dose or as a daily dose (0.2, 0.6, and 1.5 mg/kg) for 30 days. The blood and organ concentrations of the arsenic species, including As(III), dimethylarsinic acid (DMA), and monomethylarsonic acid (MMA), were studied on day 1 (single- dose study), day 30 (multiple dosing study), and day 60 (reversibility study). As(III) was the major detectable arsenic species in the blood. The pharmacokinetic parameters (total clearance, area under the curve, etc.) for As(III) indicated a limit for the capacity to eliminate As(III) at the dose of 1.5 mg/kg, and were quite the same after a single dose or chronic multiple dosing. In tissues, DMA was found to be the major metabolite and the concentrations of DMA, As(III), and MMA in general increased with the dose, with the increase most significant at a dose of 1 .5 mg/kg. However, normalized tissue distribution of As(III) in the kidney on day 1, but not on day 30, was nonlinear. Along with decreased levels of As(III) and increased levels of DMA , an inducible capacity for methylating As(III) to DMA after chronic dosing in kidney was suggested. The tissue concentration of DMA was highest in lung and liver, and the normalized tissue distributions in liver on day 30 were nonlinear, suggesting a limit in eliminating DMA after a chronic high load of As(III) . Tissue concentrations of As(III), DMA, and MMA in bladder increased dramatically after chronic dosing. However, after washout for 30 days, As(III), DMA, and

MMA were all undetectable in bladder and liver. However, As (III) in hair and low levels of DMA in lung, kidney, heart and hair were still detected. In conclusion, in rabbits we found a similar pharmacological profile after a single dose or chronic multiple dosing of parenteral arsenic trioxide, with a limiting metabolizing capacity at a dose of 1.5 mg/kg. Tissue accumulation of arsenic species, mainly DMA, and its reversibility after washout were tissue- selective. The potential for late toxicities of arsenic trioxide in organs with a significant tendency for arsenic accumulation with low reversibility should be closely monitored.

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