Effects of tetrathiomolybdate, trientine, and penicillamine on intestinal copper uptake: a randomized placebo-controlled 64Cu PET/CT study

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INTRODUCTION

In Wilson Disease (WD), ATP7B protein dysfunction leads to copper accumulation with hepatic and neurologic disease[1]. Treatments include D-penicillamine (PEN) and trientine tetrahydrochloride (TRI), which chelate Cu and cause cupriuresis, and the investigational copper binding agent bis-choline-tetrathiomolybdate (TTM)[2-4].

We hypothesized that inhibition of intestinal uptake of copper could be an additional mechanism of action for these drugs. We used PET/CT to investigate the effects of TTM, TRI, PEN and placebo (PLA) on intestinal ^{64}Cu uptake. The study was conducted in healthy volunteers as ATP7B is not involved in intestinal copper absorption.

AIM

To investigate the effects of different copper chelators on intestinal copper absorption.

Due to effective first-pass copper metabolism in the liver, liver SUV reflects intestinal uptake of orally ingested ^{64}Cu.

RESULTS

Compared to pre-treatment levels:

- Hepatic ^{64}Cu levels measured 1h post-^{64}Cu dose:
  - TTM: Reduced by 92% (p<0.02). TRI: Reduced by 75% (p<0.02)
    PEN: Reduced by 23% (p=0.16). PLA: Reduced by 3% (p=1.00)
- Hepatic ^{64}Cu levels measured at 15h post-^{64}Cu dose:
  - TTM: Reduced by 82% (p<0.02). TRI: Reduced by 50% (p<0.02)
    PEN: Reduced by 31% (p<0.04). PLA: Increased by 12% (p=0.16)
- Biliary copper excretion was seen in the healthy volunteers in the TRI, PEN and PLA, but was eliminated by TTM.
- TRI reduced blood ^{64}Cu activity at 1h and 15h (p<0.03 at 15h).
- TTM reduced hepatic ^{64}Cu activity by 80-90%, but blood activity was only 40% less at 15h, indicating reduced hepatic clearance. No compensatory increased ^{64}Cu activity was detected in other organs.
- PEN and PLA did not affect ^{64}Cu activity in blood.
- In summary, after TTM:
  - Smaller percent of ingested ^{64}Cu dose present in blood and liver.
  - Absent in bile.
  - Not increased in other organs, indicating significant inhibition of intestinal ^{64}Cu absorption.

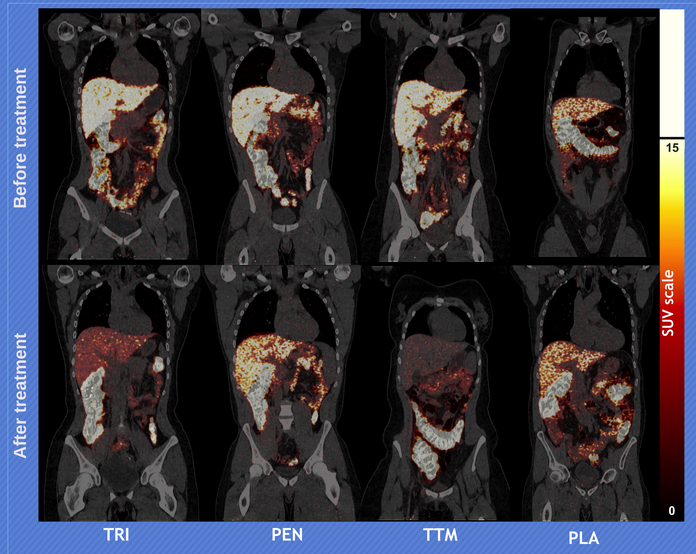


Figure 1: Representative fused coronal PET/CT scans per treatment group, before and after treatment. 15h post-^{64}Cu dose.

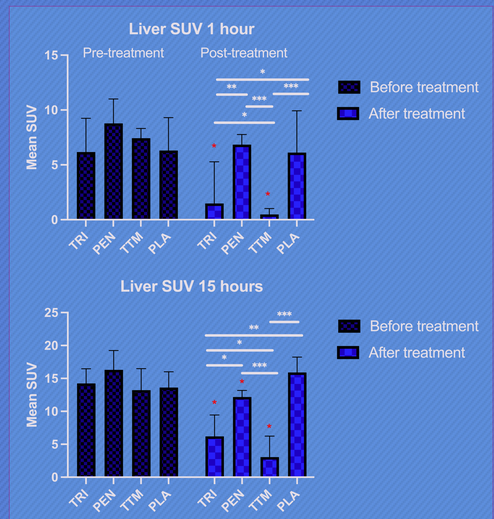


*Figure 2: Liver SUV 1H and 15H after an oral ^{64}Cu dose, before and after treatment. * (p<0.05), ** (p<0.01), *** (p<0.001). Red * (p<0.05 before vs after treatment)*

METHODS

Individualized diet 30H before oral ^{64}Cu. Fasting 6H before 1H scan.

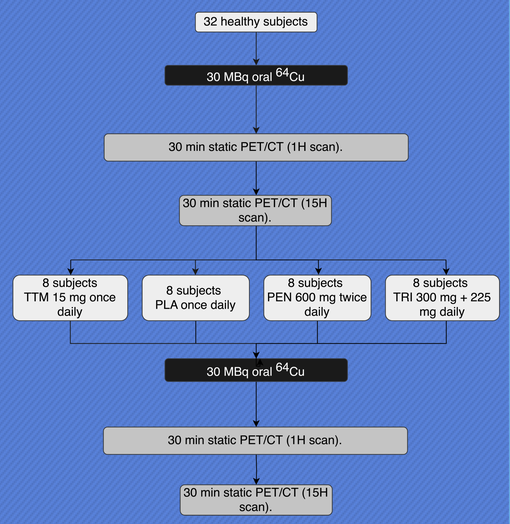
Continue individualized diet. Fasting 6 hours prior to 15H scan.

Randomization 1:1
Double blind between TTM and PLA

Fasting 1H before and after study medication ingestion.

Individualized diet 30H before oral ^{64}Cu. Fasting 6H before 1H scan.
Final medication dose 1H before oral ^{64}Cu.

Continue individualized diet. Fasting 6 hours prior to 15H scan.



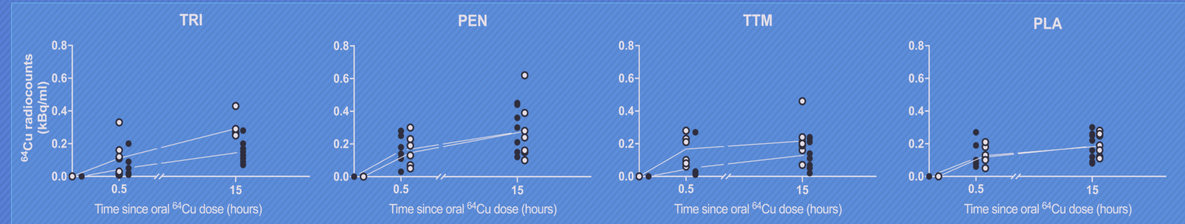


Figure 3: Venous ^{64}Cu before and after treatment.

CONCLUSIONS

- Trientine and tetrathiomolybdate, but not penicillamine inhibit intestinal copper uptake.
- This may explain recent observations of more urinary copper excretion with penicillamine but equal efficacy in treating WD patients.
- Separate 24h-U-Cu targets for trientine should be developed.
- TTM markedly reduced hepatic ^{64}Cu uptake, reducing both intestinal absorption and hepatic clearance by TTM-Cu-albumin complex formation.

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