

Cobalt protoporphyrin as a potential therapeutic agent?

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Shan *et al* have recently investigated the role of Bach1 and Nrf-2 in up-regulation of heme oxygenase-1 (HO-1) by cobalt protoporphyrin (CoPP) in Huh-7 cells (1). The authors could demonstrate the repression of Bach1 and up-regulation of the Nrf-2 protein by posttranscriptional sites of action. These data obtained in a human liver cell culture system are of high relevance for the understanding of HO-1 up-regulation by CoPP. In the abstract and discussion section, the authors state that “cobalt protoporphyrin might be considered as a potential therapeutic agent where HO-1 upregulation is desired.” As noted by the authors, CoPP is regarded as the most potent metalloporphyrin inducer of HO-1 identified so far. In addition, numerous publications have shown marked protective effects of HO-1 induced by CoPP in various experimental *in vivo* and *in vitro* models (2). Nevertheless and despite these impressive experimental data, CoPP treatment has also a number of side effects which often are not considered. As already noted by Shan *et al*, CoPP administration can lead to a depletion of hepatic cytochrome P450 levels and induce weight loss in animals (3, 4). Furthermore, CoPP suppresses thyroid and testicular hormone concentrations in serum, affects copper metabolism, elevates plasma ceruloplasmin levels, and has many other side effects (5, 6). In addition, our own unpublished results reveal that a single injection of 5 mg/kg CoPP, which is the most established experimental dose for *in vivo* experiments conferring protection in a multitude of experimental models, could have at least transient toxic effects on hepatocellular integrity as shown by increased GPT and LDH serum levels 24 hours after treatment in rats. In addition, administration of at least 2.5 μ M CoPP in *in vitro* experiments can lead to a significant LDH release, indicating cytotoxicity. All these demonstrated adverse effects of CoPP in animal and cell culture experiments might have been the reason why CoPP so far has not been used as a therapeutic agent in clinical studies in humans.

As an alternative for such studies we point to our own recent results on volatile anesthetics (isoflurane, sevoflurane) as potent inducers of HO-1 in the rat liver (7). Up-regulation of hepatic HO-1 by isoflurane exerts beneficial effects under normal and pathological experimental conditions (8, 9). These compounds are approved pharmacologic agents that are used in patients for induction and maintenance of general anesthesia

and the therapy of severe asthmatic events because of their bronchodilatory potency. Furthermore, adverse side effects of these compounds are rare and well characterized, because of their frequent usage in daily clinical anesthesia practice for more than 30 years. These substances would therefore be a realistic alternative for a possible HO-1 induction in humans.

Thus, we have recently initiated an approved clinical trial to evaluate this hypothesis. EJ

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