Abstract

Development of novel and safe therapeutic agent requires prediction of adverse effects at an early stage so as to avoid unwanted effects in humans. This necessitates continuous development and employment of newer methods of toxicity evaluation with high sensitivity and exceptional predictive capacity. In this regard the integration of high throughput technologies along with informatics tools in safety evaluation has made an important impact on the drug development process. In the present study, DNA microarray technology was used in conjunction with already established methods of toxicity evaluation to predict adverse effects in mice liver following acute dosing to 8-aminoquinoline derivatives. Two derivatives of 8-aminoquinoline used in this study are primaquine and bulaquine (CDRI 80/53), both of which have excellent anti-relapse anti-malarial properties that helps to combat liver stages of the *Plasmodium*. However, previous work (mostly biochemical) conducted on various animal models have found bulaquine to be 3-4 time safer than primaquine which is a well established anti-malarial in clinical setup. Therefore, equimolar and acute doses of primaquine and bulaquine (greater than normal therapeutic doses) were used to find target organ response at histological, biochemical, chromosomal and transcript level at different time points within 24 hours after drug administration.

Our results showed no appreciable gross abnormality at tissue or chromosomal level, however, DNA microarray based gene expression studies revealed significant (p<0.01 and 2 fold) differential expression of important genes following administration of both the 8-aminoquinolines. Interestingly, less number of gene were perturbed by bulaquine in spite of the fact that a far greater number of probes were investigated as compared to primaquine study. These findings are thus supported by previous reports, claiming bulaquine to be safer than primaquine. Furthermore, in this study two well known hepatotoxicants namely, acetaminophen and carbon tetrachloride were used and gene expression profiles were compared between hepatotoxicants and 8-aminoquinolines. Presently, no similarity was observed between hepatotoxicants and 8-aminoquinoline affected gene profiles. These observations suggest that the administration of 8-aminoquinoline derivatives does not lead to hepatic damage at doses used in the present study. However, this is the first report which shows significant hepatic tissue response following 8-aminoquinoline dosing at gene level in the absence of traditional marker of stress. This signature profile is therefore expected to help investigators in understanding metabolism and mechanism of action of 8-aminoquinoline derivatives that remains obscure till date.