

The concentration of three anti-seizure medications in hair: the effects of hair color, controlling for dose and age

## ABSTRACT

There does not appear to be any relationship between carbamazepine concentration and hair color. There is a weak relationship between hair color and valproic acid concentration, which the data suggest may be mediated by age. There is a significant, moderate relationship between phenytoin concentration and hair color such that darker colored hair has greater concentration values than lighter colored hair.

## INTRODUCTION

Background The use of hair assays in order to assess the presence of ingested chemical materials has been used in a wide variety of applications. Hair has been utilized, for example, in determining the degree of exposure to heavy metals in both post mortem and living subjects. In recent years there has been considerable focus on the recovery of illicit psychoactive substances and their metabolites from hair. Others have reported on a wide variety of substances that can be recovered from human hair samples and can be quantitatively determined. These include nicotine and cotinine, caffeine, antipsychotics and anti-anxiety medications, various antibiotics, pesticides, digoxin, and steroids. There are several advantages to hair as a sample for analysis, but the single most important attribute is undoubtedly the long retrospective time frame to which analysis of a segment of hair corresponds. This permits an evaluation of a history of exposure that is not possible with specimens such as saliva or urine. A three-centimeter length of hair corresponds, on average, to approximately 90 days of past time or "history". For compounds that are stable when sequestered in hair this represents a very desirable property. This enhanced temporal capacity lends itself to the possibility that hair analysis can be utilized to evaluate individual compliance for substances that are taken on a regular basis, such as anti-clotting medications, antibiotics, and anti-epileptic drugs. This can be an important diagnostic and assessment aid in medical practice and clinical evaluation of drug efficacy. Williams, for example, has advocated the use of hair analysis as a method for assessing therapeutic compliance to anti-seizure drug regimens. It has been well demonstrated that the major antiepileptic medications, phenytoin (PHT), carbamazepine (CBZ), and valproic acid (VPA) are readily recovered and quantified from hair specimens [1]. Thus, assessing the presence and quantity of these substances in hair may be a reliable marker for consumption, and provide an additional source of information to the physician who has historically relied only on the patient's self-reported compliance. Whether hair analysis can be an effective indication of patient compliance is controversial, however. It is widely accepted that the qualitative presence of these compounds can be reliably demonstrated by hair analysis. The controversial aspect is primarily based on the issue of whether the quantitative value of the assay can be a reliable indicator of dose. That is, is there a reliable dose/assay correlation? Tracqui et al., for example, have argued that hair analysis has value for qualitative evaluation of drug use, but is "worthless" for quantitative assessment of patient compliance. Williams (1999), however, argues the opposite, and presents data for a controlled inpatient population taking CBZ which shows remarkably good consistency between dose and assay outcome. Furthermore, Williams suggests that compliance is best measured by using patients as their own control. This is done by comparing any given assay outcome to a ground state value. So hair will show a relative change in

concentration. It is generally accepted that specific quantitative values related to a specific dose can not be applied across study subjects due to substantive individual biovariability. One issue that is not clearly understood is the variety of factors influencing the considerable biovariability that appears between persons given identical dosages of these drugs. Clinicians generally recognize that a very large number of factors can influence the drug concentration in any analytic matrix. One potential advantage of hair specimens is they may represent a relatively stable matrix over a relatively long time frame. Tracqui, even in rejecting the utility of quantitative compliance monitoring in this context, notes that a number of studies reported significant strong correlation between dose and assay outcomes for a number of different compounds, with Pearson's  $r$  ranging from .772 to .868. Another aspect of this interpretation controversy concerns whether there are systematic influences on drug concentration in hair because of color variations, differences in cosmetic treatment, and different intensities of hair hygiene. Another part of the controversy is problems related to the dependency on the accuracy self-reported patient compliance (which may or may not be accurate), and - in the case of illicit drugs - the purity and actual contents of drugs reported as consumed. The attending physicians for these patients were queried on the confidence they had on their patient's compliance, and in general they rated the compliance as good, with only a small number of missed doses. However, we recognize that there are reliable data to indicate that patient compliance to anti-seizure medication regimens may be weak, and a delimitation of this research is that there was not rigid control of patient compliance. One of the general weaknesses characterizing much of the analysis of hair assay data has been the inadequacy of the statistical models used to assess the experimental information. Oftentimes claims or conclusions are derived from experimental data that is not supported by statistical analysis. In some cases, in fact, analyses of the data show that the conclusions reached are clearly incorrect. There has been, in general, a failure in the assessment of experimental hair analysis data to use appropriate available statistical procedures, or to assess whether the critical assumptions that underlay statistical procedures are met by the data. And almost without exception, there has been no utilization of more sophisticated and sensitive statistical techniques that are available to examine multivariate phenomena. This is true even though there is a general recognition that the relationship between dose and assay are likely to be mediated by a complex series of intervening events and are particularly appropriate to this analytic approach.

## CONCLUSION

**Conclusions** This assessment of the recovery of three compounds, CBZ, VPA, and PHT, from hair samples identifies a variable effect of hair color on assay concentration by drug type. The generalized hypothesis assessed is that darker coloration of hair is associated with a greater concentration of analyte in the hair. For CBZ, hair color does not appear to exert a significant effect on the quantity of the compound recovered from hair. For VPA there appears to be a very weak color effect, but the number of light-haired subjects attenuates the strength of the conclusion. For all drugs there appears to be a significant positive relationship between dose and hair concentration. We also suggest that for VPA there appears to be effects of collinearity between age and hair color, and possibly dose and hair color. Both of these phenomena could produce confounding effects in trying to describe the dose/assay relationship. The limitations of the data are that the subjects are a clinical, non-random, population and the range of dosages across all color grouping was not uniform, nor was dosage

duration. Furthermore, the number of light hair subjects was, for certain drugs, very small.