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Pharmacokinetics of the *S*- and *R*-enantiomers of aminoglutethimide in saliva of breast cancer patients: correlations with plasma

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The development of sensitive analytical techniques such as HPLC and enzyme immunoassay have permitted measurement of very small quantities of drugs in biological fluids. These techniques have been applied to measure drug concentration in human saliva mainly because it is easily accessible by noninvasive methods and has an extremely low protein content compared with plasma. Thus saliva is suitable for indirectly measuring free drug concentrations in plasma in cases where the salivary drug concentration has been shown to be predictably related to the free drug concentration in plasma. Although a preliminary study in man detected the aromatase inhibitor aminoglutethimide (AG) and one of its metabolites, acetyl aminoglutethimide (AcAG) in saliva, there has been no systematic study of this aspect of the disposition of the drug.

After collection, the saliva sample can be stored frozen (to inhibit bacterial growth) until required or it may be assayed immediately. The protein and particulate matter in saliva can be separated by centrifugation but it is important to establish the extent of binding, if any, to this fraction for each individual drug. If binding is considerable, it is necessary to adopt a standard technique such that all saliva samples are prepared for assay in an identical manner. As the binding of racemic AG to plasma proteins is low and readily reversible, binding of AG in saliva was considered not to be a problem. The detailed results for the concentrations of R- and S-AG (determined by HPLC; Alshowaier et al 1995) in the saliva of six patients with advanced breast cancer receiving racemic AG (500 mg, orally), showed zero values in some samples, similar to that noted for plasma levels. While this was found only in one patient (#4) for R-AG, S-AG could not be detected in any of the samples of this patient. Zero values were also obtained for S-AG in the 4, 8, 36 and 48 hr samples from patient #1 and in the 12 and 36 hr samples from patient #6. In contrast, AcAG was detected in all samples of saliva except the 48 hr sample from patient #3 (R-AcAG). This raises the question of the reliability of the assay, in this instance for R- and S-AG in saliva. In this connection, it is interesting to observe that when means are calculated on the basis of the assay results (i.e. zero values included), the mean concentration ratio R-AG/S-AG for saliva is about 1.8. If the means are calculated omitting the zero values, the ratio is about 1.0 Using the data for AcAG, the concentration ratio R-AcAG/S-AcAG is approx 1.0. Thus this could also be indicative of a problem with the assay applied to saliva. However, it was noted that recoveries of all the AG standards from saliva were highly reproducible. Analysis of variance between the data for plasma (4-48 hr) and saliva levels indicated that, for both R-AG and S-AG, there were no significant differences ($P>0.2$) between the concentrations in these two body fluids. In contrast, for both R-AcAG and S-AcAG concentrations in saliva were always significantly higher than in plasma ($P<0.001$). However, no statistically significant correlations between the above comparisons were found, unlike the highly significant correlations that have been found between salivary and plasma levels of carbamazepine, phenobarbitone, phenytoin and primidone. The salivary data, were also grouped on the basis of acetylator phenotype. Of all the possible combinations of comparisons, the only one to be significant ($P=0.002$, ANOVA) was between the fast and slow acetylators for the levels of R-AG (slow>fast). This is similar to the observation made for plasma levels of R-AG in fast and slow acetylators, although in that instance it was not a significant ($P>0.05$)) difference. Overall, the saliva data indicate that determining the concentration of either AG or AcAG enantiomers (or racemate) is an inappropriate substitute for monitoring their concentrations in plasma.

Alshowaier, I et al (1995) Ther Drug Monit, 17, 538-543.