

Acetylator phenotype on the disposition of aminogluthethimide.

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Abstract:

Aminogluthethimide (AG) 500 mg was administered orally to four normal volunteers and eight patients undergoing treatment for metastatic breast cancer. In each subject the acetylator phenotype was established from the monoacetyldapsone (MADDS)/dapsone (DDS) ratio. Acetylamino-gluthethimide (acetylAG) rapidly appeared in the plasma and its disposition paralleled that of AG. A close relationship (P less than 0.01) was observed between the acetyl AG/AG and MADDS/DDS ratio suggesting that AG may undergo polymorphic acetylation like DDS. AG half-life was 19.5 ± 7.7 h in seven fast acetylators of DDS and 12.6 ± 2.3 h in five slow acetylators and its apparent metabolic clearance was significantly (P less than 0.01) related to the acetylAG/AG ratio. Over 48 h the fast acetylators excreted $7.7 \pm 4.4\%$ of the administered AG dose in the urine as unchanged AG as compared to $12.4 \pm 2.8\%$ in slow acetylators. A much smaller fraction of the dose was excreted as acetylAG: $3.6 \pm 1.5\%$ by fast and $1.9 \pm 1.0\%$ by slow acetylators respectively. After 7 days treatment with AG at an accepted clinical dose regimen to the eight patients there were significant reductions in the half-lives of AG (P less than 0.01) and acetylAG (P less than 0.01) and a trend (0.1 greater than P greater than 0.05) towards reduction of the acetylAG/AG ratio which became significant (P less than 0.05) if the one patient on a known enzyme inducer was omitted. The mean apparent volume of distribution was not significantly (P greater than 0.1) altered but the mean apparent systemic clearance of AG was increased (P less than 0.05). These changes are attributed to auto-induction of oxidative enzymes involved in AG metabolism.