

## Aminopyrine demethylation kinetics: comparison of plasma and exhaled metabolites

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Aminopyrine (AP) is metabolised by two successive N-demethylations to give monomethylaminoantipyrine (MAP) and aminoantipyrine (Brodie & Axelrod, 1950). Following demethylation the single carbon moiety enters the formaldehyde-formate pool and is exhaled as  $\text{CO}_2$ . Hence  $\text{N-}^{14}\text{CH}_3$  groups yield  $^{14}\text{CO}_2$  which provides a convenient non-invasive method of monitoring the metabolism of aminopyrine in man (Hepner & Vesell, 1974) and animals (Lauterburg & Bircher, 1976).

We have developed a technique for continuous determination of  $^{14}\text{CO}_2$  exhalation in the rat (Sprague Dawley) following  $[^{14}\text{C}]$ -AP administration (30 mg/kg; i.p.). As shown in Figure 1, the  $^{14}\text{CO}_2$  formation rate-time plots peak rapidly and decline in a biphasic fashion. The latter phenomenon has apparently not been observed by previous investigators. By means of curve stripping, half-life ( $T_{1/2}$ ) values (min) are assigned to the initial ( $\alpha = 40 \pm 14$ ,  $n = 8$ ) and terminal ( $\beta = 116 \pm 28$ ,  $n = 8$ ) phases. The insert shows the plasma concentration-time plots for AP ( $T_{1/2} = 48 \pm 12$ ,  $n = 6$ ) and MAP ( $T_{1/2} = 122 \pm 32$ ,  $n = 6$ ).

Pretreatment with either an enzyme inducer (phenobarbitone, 100 mg/kg for 4 days,  $n = 4$ ) or inhibitor (SKF 525A, 50 mg/kg 1 h prior to AP administration,  $n = 4$ ) has dramatic effects on both the  $^{14}\text{CO}_2$  and plasma data. There is a statistically significant ( $P < 0.05$ ) decrease in the  $T_{1/2}$  values for  $\alpha$  ( $29 \pm 10$ ),  $\beta$  ( $64 \pm 30$ ), AP ( $27 \pm 4$ ) and MAP ( $47 \pm 6$ ) after phenobarbitone pretreatment. In the inhibition studies only one phase is apparent in the  $^{14}\text{CO}_2$  formation rate-time plot ( $T_{1/2} = 591 \pm 222$ ). The plasma AP  $T_{1/2}$  shows a statistically significant ( $P < 0.01$ ) increase to  $298 \pm 17$ . No MAP  $T_{1/2}$  could be calculated since plasma concentrations did not peak within four hours.

These results suggest that AP is demethylated at a faster rate than MAP and illustrate the need to consider both sources of  $^{14}\text{CO}_2$  in aminopyrine breath analysis studies.

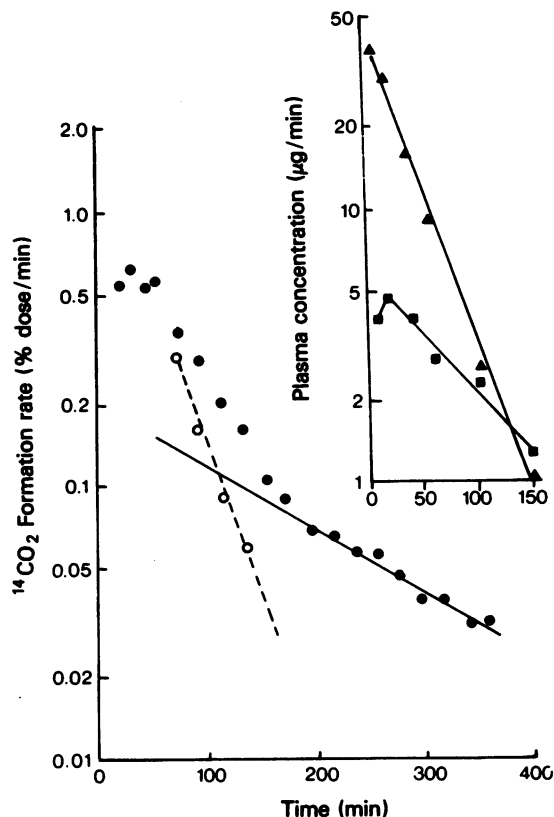


Figure 1 A typical  $^{14}\text{CO}_2$  formation rate-time plot following administration of  $^{14}\text{C}$ -aminopyrine; observed data points (●) and stripped  $\alpha$  phase data points (○). The insert shows a typical plasma concentration-time plot for aminopyrine (▲) and monomethyl-aminoantipyrine (■) following aminopyrine administration.

### References

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