ANTIPYRINE KINETICS IN CANNABIS SMOKERS

Cannabis (delta-9-tetrahydrocannabinol or delta-9 THC) has evoked considerable interest as a social drug (Wig & Varma, 1977). Since the use of cannabis presents a rapidly growing problem in our society it was thought worthwhile to study the effect of cannabis on antipyrine kinetics. A study was carried out on seven subjects who had smoked approximately 27 g of cannabis daily for the last 2–6 (3.86 ± 1.35) years. It was very difficult to find subjects who were addicted only to cannabis smoking and out of seven subjects six had also smoked 6–10 (mean ± s.d.; 7.5 ± 1.64) cigarettes a day for the same period.

Male volunteers between 25–35 years residing in Chandigarh who had never taken alcohol or opium and were not on any medication during the period of the study comprised the sample. The method followed for the collection of samples and estimation of antipyrine levels has recently been described (Uppal, Garg, Sharma, Nair & Chaudhury, 1980). Each subject received an oral dose of 18 mg/kg antipyrine with a glass of cold water containing 1 g of glucose after an overnight fast. Blood samples were collected at 0, 2, 4, 8 and 12 h. The estimation of haemoglobin, plasma bilirubin, plasma glutamic pyruvate transminase, plasma alkaline phosphatase, plasma creatinine, serum protein, albumin and globulin was carried on the sample collected at 0 h, while 2, 4, 8 and 12 h plasma samples were stored at −20°C until assayed spectrophotometrically for antipyrine (Brodie & Axelrod, 1950).

Antipyrine half-lives were estimated by least squares regression analysis of the log plasma concentration-time plot. The calculations were based on the assumption that the kinetics of antipyrine are adequately explained by a one compartment open model with first order elimination kinetics. The antipyrine half-life in the seven subjects were 5.6, 4.8, 5.3, 2.7, 3.6, 4.9 and 2.5 h. The mean antipyrine half-lives in cannabis users obtained in this study had been compared to earlier published results on controls and smokers in Table 1. The results were analysed statistically using Student's *t*-test.

These results indicate clearly that cannabis smoking significantly reduces the antipyrine elimination half-life. The mean half of 4.17 ± 1.25 h is significantly lower ($P < 0.05$) than 9.25 ± 2.8 h observed in controls and 6.27 ± 1.9 seen in cigarette smokers. The mean cigarette consumption of the cigarette smoking group was 21.1 cigarettes a day with a standard deviation of 6.97 and the mean duration of smoking 13.2 ± 3.73 years. The aV_d (apparent volume of distribution) in the various subjects does not show much change but the MCR (metabolic clearance rate) is significantly higher in cannabis smokers when compared to controls.

The decreased antipyrine half-life observed in cannabis users is probably due to induction of hepatic microsomal enzymes. The fact that the half-life observed in cannabis users was significantly lower than that in smokers indicates that cigarette smoking and cannabis smoking were probably producing an additive effect by inducing the same enzyme systems.

These observations indicating enzyme induction are similar to those obtained by Jusko, Schentag, Clark, Gardner, Yurchak (1978) who demonstrated that the half-life of theophylline was reduced from 8.11 h to 5.87 h in marihuana users and to 5.73 h in tobacco users and 4.03 h in subjects who had used both tobacco and marihuana. Again, in a recent study Fraser & Dotson (1980) have confirmed that the antipyrine half-life of 15.3 h was reduced to 13.1 h in smokers and 8.1 h in marihuana and cigarette smokers.

Benowitz & Reese (1977) have shown that there is an increase in antipyrine half-life in subjects who orally ingested THC. The difference between these results and the results reported in this paper could be due to the fact (a) that oral ingestion of THC has a different effect than when smoked, or (b) that THC effects are not the same as cannabis.

In addition to the studies described, the antipyrine clearance was calculated in two subjects who had a history of drinking a decoction made from 80–100 g of the leaves of cannabis every day for 3–8 years. These persons were not smoking either cigarettes or cannabis. The antipyrine half-life was 3.2 h and 8.9 h respectively. It is important to keep in mind the significant enzyme inducing properties demonstrated by

Table 1 Antipyrine kinetics in three groups of subjects (mean ± s.d. values)

Type of subjects	*Number of subjects*	$T_{1/2}$ *(h)*	aV_d *(l/kg)*	*MCR (ml min^{-1} kg^{-1})*
Controls	9	9.25±2.8	0.45±0.14	0.63±0.30
Cigarette smokers	10	6.27±1.9*	0.44±0.22	0.84±0.36
Cannabis smokers	7	4.17±1.25**	0.54±0.18	1.00±0.21***

* Differs significantly from controls at $P < 0.05$.
** Differs significantly from controls and cigarette smokers at $P < 0.05$.
*** Differs significantly from controls at $P < 0.05$.

cannabis smoking when prescribing drugs to such patients.

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SHOULD CLEARANCE BE NORMALISED TO BODY SURFACE OR TO LEAN BODY MASS?

In 1928, McIntosh, Möller & Van Slyke concluded that urea clearance values in children (8 children aged 3 to 12 years), when normalised to 1.73 m^2 body surface area (BSA), fell within the range of clearances observed in normal adults (60–100 ml min^{-1} 1.73 m^{-2} BSA). Normalisation of renal, hepatic or body clearance values to 1.73 m^2 BSA have since become a standard method.

As part of a study in which we examined the feasibility of a method for the estimation of serum half-lives of drugs from creatinine clearance, we were unable to confirm these findings. When the means of 11347 creatinine clearances (CCr) of 5146 normal subjects (68 publications, reference list available from the authors on request) were plotted as a function of age (Figure 1), the CCr of children (1 to 30 days, 8 to 18 years) did not fall within the CCr (35–110 ml min^{-1} 1.73 m^{-2} BSA) observed in normal adults. It can also be seen that a unique normal clearance range for all ages, which was the original aim of McIntosh *et al.* (1928) is not realistic. According to the patient's age, 60 ml min^{-1} 1.73 m^{-2} BSA should be regarded one time as a normal renal function, another time as a decreased or sometimes even as an increased renal function.

In our study, we looked for a normalisation of a clearance in order to obtain for a same clearance value, a same drug half-life, independent of the age of the subject. When CCr was expressed in ml/min or in ml min^{-1} 1.73 m^{-2} BSA, quite different half-lives for gentamicin (Nunnery & Riley, 1969; McCracken & Jones, 1970; McCracken, Chrane & Thomas, 1971; McCracken, 1972; Matzetti, Konca, Panero & Orzalezi, 1973; Paisley, Smith & Smith, 1973; Simon, Schmitt, Malerczyk & Arkenau, 1973; Siber, Echeverria, Smith, Paisley & Smith, 1975) were observed in several age groups compared to half-lives in adults with the same CCr (Table 1). Similar data can be presented for other drugs e.g. amikacin, ampicillin, carbencillin, cefazolin, tobramycin, etc. This is not surprising as CCr in ml min^{-1} or in ml min^{-1} 1.73 m^{-2} BSA is not related to the distribution volume (V_d) of the drug. However, the package insert of many drugs still recommends CCr in ml min^{-1} as a guide for drug dosage adjustments in renal impairment. Sometimes these inserts do not even mention that the guidelines should only be used in adults. In fact, until this paper, no dosage rules were available for neonates and children with renal dysfunction. The more the individual V_d differs from the mean V_d for adults, the more absurd calculated drug half-lives or dosage guidelines will be obtained. Only when clearance is normalised to a standard V_d, will similar drug half-lives in adults and children correspond with identical clearances. For example in the case of CCr, the V_d of creatinine is equal to the total free body water (Dominguez, 1950). Furthermore, the latter is a constant part of 72% (± 1%) of