Pharmacokinetics of antipyrine in epileptic patients

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The pharmacokinetics of antipyrine were examined after oral and intravenous administration to 20 epileptic subjects receiving antiepileptic drug therapy. Bioavailability was essentially complete (mean bioavailability $101.2\% \pm 14.4$ (s.d.)) indicating that even in enzyme induced subjects, antipyrine behaves as a restrictively eliminated compound with negligible presystemic elimination in the gut or liver. Of the generally used measures of enzyme induction (oral clearance, oral half-life and intravenous half-life) oral clearance was the most closely related to the intravenous clearance of antipyrine ($r = 0.919$, $P < 0.001$). Oral antipyrine administration is an alternative to intravenous administration in epileptic subjects who are enzyme-induced.

Keywords antipyrine enzyme induction oral clearance

Introduction

Antipyrine has been used extensively as a model drug to study the induction or inhibition of oxidative drug-metabolizing enzymes (Vessel, 1979; Park, 1982). It is suitable because it is rapidly and completely absorbed from the gastrointestinal tract and distributed in total body water with only a small degree of tissue plasma protein binding. It is metabolized almost completely with negligible renal elimination of unchanged drug. Because of the low pKa (1.4) of antipyrine and its small degree of plasma protein binding, saliva antipyrine concentrations are closely related to plasma concentrations. It is possible, therefore to predict plasma antipyrine kinetics from saliva samples which is much more acceptable than venepuncture to volunteers (Fraser *et al.*, 1976).

Over recent years, studies of antipyrine kinetics in enzyme-induced subjects have used either oral (Roberts *et al.*, 1976; Perucca *et al.*, 1984; Bennett *et al.*, 1982; Pessayre *et al.*, 1978) or intravenous (Perucca *et al.*, 1980) antipyrine administration. It has not been directly demonstrated whether the antipyrine bioavailability

was complete in the oral studies or whether significant presystemic elimination occurred in the gut. Because oral antipyrine clearances (Roberts *et al.*, 1976) and half-lives (Brooks *et al.*, 1976) have been used as measures of hepatic antipyrine elimination, we decided to determine which of these most closely reflected the intravenous clearance in enzyme induced subjects.

Methods

Twenty epileptic subjects (14 male) aged between 16 and 60 years (mean $\pm$ s.d. = 34.2 ± 12.9 years) gave informed consent to participate in the study. The protocol was approved by the Hospital Ethics Committee. All subjects had been taking one or more of the following antiepileptic drugs and the doses were not altered in the previous 3 months or during the course of the study: carbamazepine, phenytoin, phenobarbitone and primidone. None of the patients had any known endocrine, neoplastic, cardiac, hepatic or renal disease. Alcohol intake and smoking

habits varied amongst the subjects but were constant within subjects during the period of the study.

Antipyrine 600 mg dissolved in 100 ml of orange juice was administered orally after an overnight fast. Food was not allowed for 3 h following drug administration. Mixed stimulated (by chewing Teflon tape) saliva samples were obtained at times 0, 1, 2, 3, 5, 8, 13, 24 and 32 h. Because antipyrine itself has been demonstrated to be a milder inducer of hepatic enzymes (Ohnhaus *et al.*, 1979) the second antipyrine test was performed at least 2 weeks but not more than 8 weeks later. On this occasion 600 mg of antipyrine in 50 ml normal saline was given by intravenous infusion over 5 min. Additional saliva samples were collected at 15, 30 and 45 min after the infusion because of the biphasic decline after this route (Swartz *et al.*, 1974). All saliva samples were stored frozen at -20°C until analysed.

The concentration of antipyrine in the saliva samples was measured by gas-liquid chromatography according to the method of Lindgren *et al.* (1974). Within batch coefficient of variation of the assay was 2.7% and the lower limit of sensitivity was 0.5 mg l^{-1} . Antipyrine half-life was calculated for each subject using all data points after 2 h. Area under the curve was calculated using the trapezoidal method and bioavail-

ability was calculated by dividing the AUC_{po} by the AUC_{iv} . The relationships between variables was examined using linear least squares regression analysis. In all cases $P < 0.05$ was taken as the minimum level of statistical significance.

Results

The bioavailability of oral antipyrine in this group of enzyme-induced epileptic subjects was shown to be essentially complete (mean bioavailability $\pm$ s.d. = $101.2 \pm 14.4\%$) (see Table 1). The mean clearance of antipyrine was $107 \pm 36\text{ ml min}^{-1}$ by the intravenous route and $109 \pm 38\text{ ml min}^{-1}$ by the oral route. The mean half-life of antipyrine after intravenous and oral administration was $6.34 \pm 3.06\text{ h}$ and $6.13 \pm 2.39\text{ h}$, respectively. There was a close correlation between intravenous clearance of antipyrine and oral clearance of antipyrine ($r = 0.919$ $P < 0.001$) (Figure 1). The slope of the relationship ($\text{CL}_{\text{po}} = 0.97 \times \text{CL}_{\text{iv}} + 5.6$) was not significantly different from the line of identity and the mean difference between paired values (a measure of bias) was -2.26 ml min^{-1} with a s.d. of $\pm 15.06\text{ ml min}^{-1}$ (a measure of precision). However, the half-life of antipyrine, whether after oral or intravenous drug administration was less closely related to intravenous antipyrine clearance ($r =$

Table 1 Antipyrine kinetic parameters in 20 epileptic patients

Patient	Oral clearance (ml min^{-1})	Half-life (h)	Intravenous clearance (ml min^{-1})	Half-life (h)	Bioavailability (%)
1	63.70	4.85	68.47	5.32	100.5
2	215.96	2.19	209.96	3.08	97.2
3	156.95	6.43	129.89	5.03	85.7
4	71.53	6.64	87.13	4.91	121.8
5	111.36	7.19	99.57	6.21	89.4
6	162.87	3.79	156.46	3.58	95.3
7	115.60	4.06	102.12	4.02	88.3
8	122.43	4.38	106.03	3.13	86.6
9	120.50	3.56	121.04	3.59	100.5
10	88.70	7.68	126.76	3.86	139.9
11	113.36	4.14	112.84	4.92	99.5
12	117.14	7.56	90.90	7.56	77.6
13	73.12	8.57	69.40	7.94	94.9
14	114.02	5.89	127.92	5.16	112.2
15	113.74	4.37	124.14	4.89	102.2
16	87.67	7.94	84.43	11.15	103.8
17	80.34	9.74	68.19	10.83	117.8
18	112.35	3.93	119.91	9.07	93.7
19	49.31	11.26	49.08	14.14	100.5
20	88.48	8.46	79.77	8.36	110.0
Mean	109	6.13	107	6.34	101.2
$\pm$ s.d.	± 38	± 2.39	± 36	± 3.06	± 14.4

Figure 1 Relationship between apparent oral and intravenous clearance of antipyrine in 20 epileptic subjects.

−0.734, and −0.668, respectively). There was a significantly closer relationship between oral and intravenous clearance than between intravenous half-life and intravenous clearance ($Z = 2.27$, $P < 0.05$) but the relationship between oral half-life and intravenous clearance, just failed to be statistically weaker ($Z = 1.87$, $P < 0.1 > 0.05$) than the relationship between oral and intravenous clearance.

Discussion

It would appear that oral antipyrine clearance closely reflects intravenous clearance in epileptic subjects since the oral bioavailability approximates to 100%. Thus there does not seem to be a significant degree of presystemic elimination in the gut or liver. Oral administration of antipyrine is obviously preferable as it is easier to perform and more acceptable to the patient, but would only be valuable if it reflected the intravenous clearance, which we took to be the reference standard. Antipyrine half-lives, whether after oral or intravenous drug administration, were

much less closely related to intravenous clearance. This is possibly because when clearance was computed all the saliva antipyrine values were used in the calculation of area under the curve. However when calculating half-life, data for the first 2 h were excluded as part of the drug absorption phase, resulting in fewer samples and greater risk of error in measurement. There is likely to be less error when clearance is used since its calculation makes use of all the data points in model-independent fashion.

Since the study was not balanced and antipyrine was always given orally first, we cannot rule out a period or order effect, but this is unlikely.

In conclusion we would suggest that oral antipyrine clearance is a convenient non-invasive guide to the degree of enzyme induction in epileptic subjects, as reflected by intravenous clearance and that bioavailability of antipyrine in enzyme induced subjects is essentially complete.

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