

## Review

# Antipyrine as a model drug to study hepatic drug-metabolizing capacity

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## Introduction

Most drugs are eliminated by hepatic biotransformation. The capacity of the enzymes involved may be assessed by studying the metabolism of a model or probe drug. Although the multiplicity of the enzymes prevents a single probe substance from predicting the metabolism of all other drugs, antipyrine has been one of the most valuable models.

Antipyrine was synthesized at the end of the last century and remained popular until the 1930s. In the late 1940s the first studies on antipyrine metabolism were performed in man [1]. The elimination half-life of antipyrine was determined and it was shown that the drug is rapidly and completely absorbed following oral administration. Its volume of distribution was the same as total body water and its elimination was almost exclusively by biotransformation. In the late 1960s and through the 1970s, antipyrine was used extensively in studies on the influence of inheritance, environmental factors and disease.

In 1973 it was hypothesized that the formation of each antipyrine metabolite is dependent on different microsomal isoenzymes belonging to the cytochrome

*P*-450 system in the liver. This hypothesis is now generally accepted.

The present review gives a detailed outline of the following:

- (1) Pharmacokinetics of antipyrine.
- (2) Designs for the estimation of antipyrine clearance, including a novel non-invasive self-conductable method.
- (3) Quantitative assessment of liver function by antipyrine clearance.
- (4) Genetic control of antipyrine metabolism.
- (5) Changes in antipyrine metabolism caused by environmental factors.
- (6) Influence of various physical conditions and diseases on antipyrine metabolism.
- (7) Interactions between antipyrine and other drugs.
- (8) Antipyrine in the future.

## Pharmacokinetics of antipyrine

After intravenous administration the decay of plasma antipyrine can best be described by a two-compartment model [2]. Antipyrine is completely

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and rapidly absorbed by mouth. Distribution takes place very rapidly, whereas elimination is very much slower [2-7]. The volume of distribution equals total body water and protein binding is negligible [1]. Irrespective of the rate of secretion and pH, saliva holds concentrations of antipyrine close to those in plasma and can act as a substitute in kinetic studies. The clearance of antipyrine is independent of liver blood flow within a dose range of 250-1000 mg [3].

Antipyrine is almost completely metabolized by hepatic cytochrome *P*-450 enzymes, leaving only a few percent to be excreted unchanged in urine [1]. About 99% of radiolabelled doses of antipyrine has been recovered in urine [4]. The excretion into urine of unchanged antipyrine and the three major metabolites (Fig. 1), *N*-demethylated, 4-hydroxylated and 3-methylhydroxylated, accounts for 65-70% of the

dose [5,6]. Minor metabolites are 3-carboxyantipyrine formed from HMA, 4'-hydroxyantipyrine and 4,4'-dihydroxyantipyrine, each accounting for 5% of the dose or less in man [5,8].

In patients with a percutaneous biliary fistula, total biliary excretion of antipyrine and its metabolites represents less than 10% of the administered dose [9]. The excretion into urine of the three major metabolites of antipyrine has been shown to reflect their rate of formation [10,11]. It is important that urine is collected for a period of at least 36 h to ensure complete collection of hydroxymethylantipyrine, the excretion of which is somewhat delayed compared with the other metabolites [5]. There is increasing evidence that the formation of each of the three main antipyrine metabolites is dependent on one or more selective form(s) of cytochrome *P*-450. The evidence

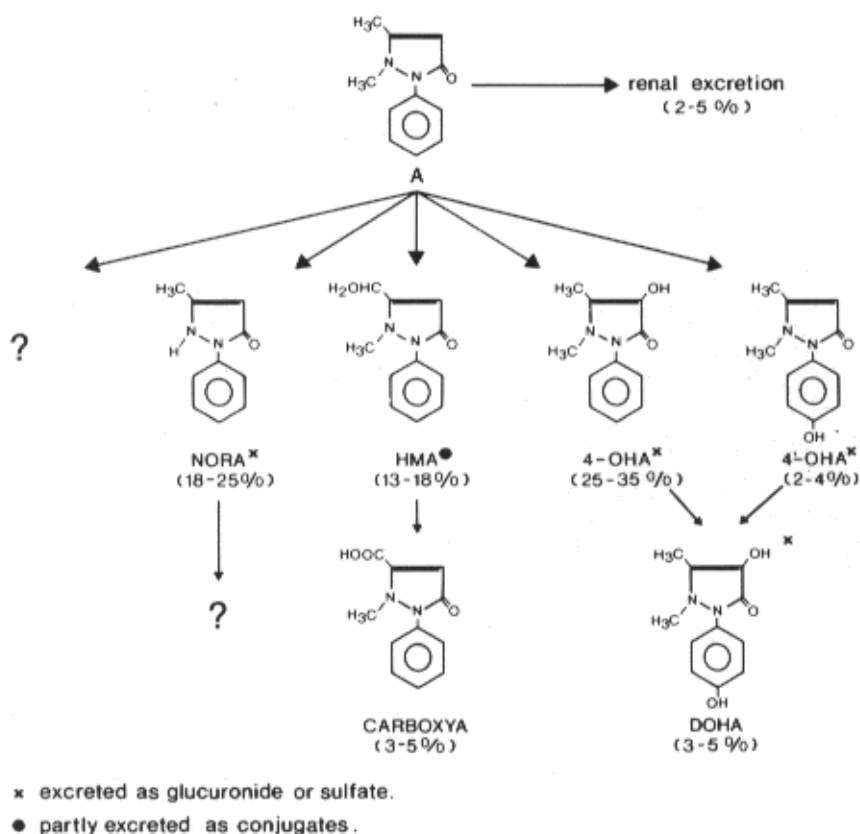


Fig. 1. Antipyrine metabolism in man. Abbreviations: A = antipyrine; NORA = norantipyrine; HMA = 3-hydroxymethylantipyrine; 4-OHA = 4-hydroxyantipyrine; CARBOXYA = 3-carboxyantipyrine; DOHA = dihydroxyantipyrine.

is mainly based on the various changes in the rates of metabolite formation observed in man after administration of enzyme-inducing agents [8,12]. Accordingly, the saliva or plasma clearance of antipyrine reflects the aggregate activity of at least three different hepatic cytochrome *P*-450 drug-metabolizing isoenzymes. The activity of each isoenzyme is assessed by multiplying the antipyrine clearance and the fraction of dose excreted as the particular urine metabolite.

#### Designs for estimating antipyrine clearance, including a novel non-invasive self-conductable method

Factors influencing the metabolism of antipyrine can be studied longitudinally, comparing measurements in subjects before and after an intervention in a paired design, or cross-sectionally, comparing two groups of subjects in an unpaired design. The intraindividual variation of the antipyrine clearance is 9–16%. A paired design with 20 subjects is able to detect a difference of 5–8% at a power of 0.8 and a one-sided level of significance of 0.05. Due to the interindividual variation of 25–40%, an unpaired design involving 20 subjects can only detect a difference of 16–25% at a similar power and significance level. As to the rate of formation of antipyrine metabolites, the intraindividual variation is 10–20% and the interindividual 40–50%. Consequently, paired designs for the study of factors influencing antipyrine metabolism are preferred whenever possible. However, a major pitfall of the paired design is the enzyme-inducing capacity of antipyrine itself [13]. Autoinduction is with certainty prevented at daily doses of 1 mg/kg or intervals of 5 days between doses of 1000 mg [13,14]. A particularly elegant paired design, involving steady-state antipyrine administration by a rectal osmotic mini-pump, has been described by Breimer and co-workers [15].

#### Determination of antipyrine clearance using a single time-concentration point

We have earlier described in detail that the clear-

ance can be determined from  $Cl = V_d [\ln(D/V_d C_t)]/t$ , where  $(t, C_t)$  is the single time-concentration point,  $V_d$  is the volume of distribution determined from body weight, body height, age and sex, and  $D$  is the dose [16,17]. Preferentially, the same sample should be taken about 24–48 h after antipyrine to ensure minimum variation; sampling too early is deleterious [16]. This is also the case for the conventional multiple-sample method [17].

We have earlier described what happens in certain situations to the clearance if  $V_d$  is biased [18]. This can be described more generally. If the bias on  $V_d$  is designated the magnitude  $B$ , the biased  $V_d$  is consequently  $B \cdot V_d$ . The resulting biased clearance is then given by

$$Cl_B = B \cdot V_d \cdot [\ln(D/V_d \cdot B \cdot C_t)]/t$$

Using  $C_t = D/V_d \exp(-k \cdot t)$ , where  $k$  is the elimination rate constant, it can be calculated that

$$Cl_B = Cl \cdot B \cdot [1 - \ln B / (k \cdot t)]$$

The relation between the one-sample clearance bias  $B$  and the ratio sampling-time/half-life is depicted in Fig. 2. For the one sample taken at the optimal time, the relation between bias on  $V_d$  and the re-

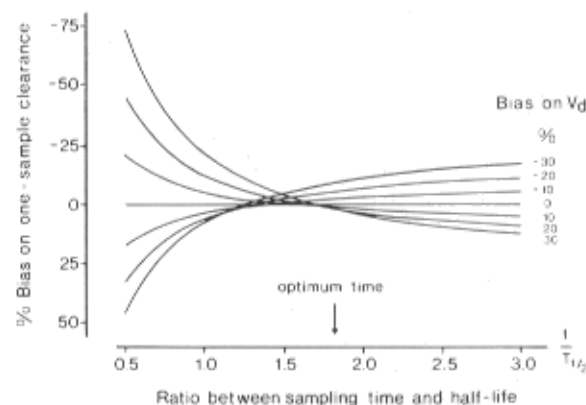
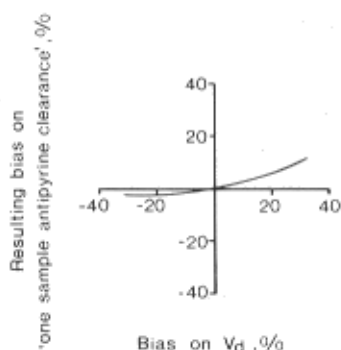


Fig. 2. Relationship between bias on the one-sample clearance, time of sampling for the one sample (given relative to the half-life), and the bias on the volume of distribution. If the bias on the volume of distribution is  $B$ , then the bias on the clearance is  $B - (B \cdot \ln B) / kT$ , where  $T$  is the time of sampling for the one sample and  $k$  is the elimination constant. For details see the text.



**Fig. 3.** Relationship between bias on the volume of distribution and the resulting bias on the one-sample clearance estimate assuming that the one sample is taken at optimal time. From Fig. 2 it can be seen that, although the optimal time of sampling is exceeded, the bias on the clearance remains small.

sulting bias on the one-sample clearance is given in Fig. 3. From these figures it is evident that a bias on  $V_d$  is deleterious if the one sample is taken earlier than at the optimal time. This emphasizes the importance of late sampling when using the one-sample technique.

Until recently, many investigators collected multiple samples for determination of antipyrine kinetics within 12 h after administration. In such cases the variation coefficient of antipyrine clearance will be at least 8%. If the half-life is 24 h and the samples are taken within 12 h, the coefficient of variation will be at least 20%. If the samples are collected optimally, i.e. spaced around  $1/k$  [17], which is 17.3 h in the first example and 34.6 h in the second, then the coefficient of variation of clearance is at best reduced to 2.5%.

#### Quantitative assessment of liver function by antipyrine clearance

Liver disease causes a sequential loss of hepatic function. It has been suggested that the 'functional hepatic mass' is reduced as the disease progresses until it reaches a minimal residual function incompatible with survival.

Eliminated almost exclusively by hepatic metabolism, antipyrine is an ideal drug to investigate hepatic

function. As intrinsic clearance is a measure of drug-metabolizing enzyme activity, this parameter is the most attractive for estimating hepatic function [19].

Quantitative assessment of liver function by antipyrine clearance is not of much diagnostic value in the initial stage of the disease. Rather, according to the concept of functional hepatic mass, quantitative assessment may be used for estimating (1) severity of disease, (2) prognosis, (3) risk (e.g., exposure to hepatotoxins), (4) time course, (5) need for treatment, and (6) results of therapy.

The prognostic value of antipyrine clearance is well established in cases of acute viral or toxic hepatitis [20]. The minimal residual function appears to be about 10–20% of the control value, which is consistent with animal experiments, where a 90% reduction in antipyrine clearance after subtotal hepatectomy has a mortality rate of about 10%.

In patients with alcoholic liver cirrhosis, antipyrine clearance is reduced compared with other measures of functional liver mass [20]. As such, antipyrine is considered to be predictive of survival of patients with liver cirrhosis; however, long-term studies are still awaited.

Liver transplantation results in increased antipyrine clearance, indicating that this treatment improves the drug-metabolizing activity in clinically stable patients [21]. The formation rates of the three major metabolites are reduced in patients with hepatic cirrhosis [22], the formation rate of norantipyrine being more reduced than the formation rates of 4-hydroxyantipyrine and hydroxymethyl-antipyrine [22]. In the latter study, however, the excretion rate of norantipyrine found in the control group is substantially higher than usually found in healthy controls.

In patients with primary biliary cirrhosis, antipyrine clearance is reduced [23].

Obstructive jaundice is accompanied by a reduction in antipyrine clearance which is relieved by internal and external biliary damage and is predictive of survival [24].

So far, these studies seem to be the only examples of determination of the effect of a treatment using antipyrine clearance. Long-lasting unconjugated hy-

perbilirubinaemia in patients with Gilbert's syndrome was not accompanied by changes in antipyrine clearance [25]; in these patients treatment with phenobarbitone increases antipyrine clearance and relieves pruritus (L. Ranek, personal communication).

Patients with primary hepatocellular carcinoma have a mean antipyrine clearance of 71 ml/min [26], which is probably somewhat higher than found in control groups.

### Genetic control of antipyrine metabolism in man

In normal subjects under carefully controlled environmental conditions, the pattern of variation in antipyrine metabolism suggests a genetic regulation [27,28]. Assuming a similar environment, the variation in antipyrine half-life as well as in metabolite formation rate constants is much smaller between monozygotic than dizygotic twins [28]. In 83 unrelated subjects, Penno and Vesell [27] found a trimodal distribution of each of the overall elimination rate constants of antipyrine and the formation rate constants of the three major metabolites. Pedigree analysis of 61 environmentally unperturbed members of 13 families according to the phenotype determined from this distribution was consistent with codominant Mendelian inheritance for the formation rate of each of the three metabolites, but not for the overall elimination rate [27]. In contrast to most other pharmacogenetic polymorphisms, the slow metabolizers were in the majority and the fast were very rare.

In 206 subjects recruited from 78 families, living under perhaps less-controlled conditions, the antipyrine clearance correlated significantly between both spouses and siblings, but not between parents and offspring, suggesting that environmental factors overruled the genetic regulations [29].

In a number of studies, the total antipyrine elimination rate has differed very little or not at all between the sexes [13,29,30]. By contrast, the formation rate of the 4-hydroxymetabolite seems to be considerably higher in women [30].

The present evidence suggests that the basic activity of the enzymes responsible for the formation of

each of the major antipyrine metabolites is under monogenic control. As the elimination of antipyrine is a result of many metabolic pathways, a possible variation in the total clearance related to this genetic regulation may easily be obscured by the influence from the environment.

### Changes in antipyrine metabolism caused by environmental factors

From a large number of studies it has become apparent that the metabolism of antipyrine is affected by many environmental factors such as diet, caffeine, alcohol, physical activity, smoking, and occupational exposure to various substances. The dietary protein content has an effect on antipyrine elimination. Thus, an isocaloric diet with a low ratio of protein to carbohydrate and fat decreases the antipyrine clearance and a high protein content increases it, whereas the total energy supply is of minor importance [31]. Similar results have been obtained from parenteral administration of nutrients, viz. a dextrose versus an amino acid solution [32]. Certain diet components, charcoal-broiled beef and cruciferous vegetables (i.e., Brussels sprouts and cabbage) have been shown to increase antipyrine clearance [33,34]. The effect of the former is probably caused by high concentrations of polycyclic aromatic hydrocarbons, and of the latter by the content of idoles. Caffeine consumption equivalent to more than five cups of coffee per day is associated with a high antipyrine elimination rate [35].

The effect of alcohol on antipyrine metabolism is rather complex. During co-administration of alcohol, yielding a blood concentration of about 0.8 g/l, the antipyrine clearance was unaltered [36]. Long-term ingestion of more than three drinks per day decreased the half-life of antipyrine [37], unless the alcohol ingestions had led to severe liver disease, thus impairing elimination [19]. Tobacco smoke has an enhancing effect on antipyrine elimination, probably due to the smoke content of polycyclic aromatic hydrocarbons [35].

Many substances encountered in the working envi-

ronment are capable of altering antipyrine metabolism [38]. Occupational exposure to pesticides, polychlorinated biphenyls, jet fuel, and halothane has been shown to increase the antipyrine clearance, whereas the organic solvents, styrene and toluene, and various mixtures have been without measurable effect. Exposure to lead and to mixtures of grinding dust, spray paint, and cleaners appears to inhibit antipyrine metabolism.

Alterations in the total antipyrine elimination rate attributable to environmental factors are usually small, about 10–30%, and do not seem to be of clinical importance. However, several synergistically acting factors may affect the drug metabolism capacity to a clinically important extent. At present there are no reports on possible differential effects of environmental factors on the different cytochrome *P*-450 isoenzymes responsible for antipyrine elimination.

#### **Influence of various physical conditions and diseases on antipyrine metabolism**

Increasing age has been shown to be associated with a decrease in antipyrine clearance [35]. However, the age-related variation in clearance only accounted for 3% of total clearance. Regular exercise enhances antipyrine clearance along with physical fitness [39]. On the other hand, bed rest for 3 days has a similar effect on antipyrine elimination [40]. The half-life of antipyrine may show some circadian variations, whereas the menstrual cycle has no effect [13].

As antipyrine is metabolized in the liver, hepatic diseases may profoundly affect its elimination. Several endocrine disorders affect antipyrine kinetics. Hypo- and hyperthyroidism decreases and increases the metabolism of antipyrine in a non-selective manner, respectively [22]. With regard to diabetes, the effect on antipyrine elimination is rather complex. Insulin-dependent diabetics seem to have increased antipyrine clearance, whereas non-insulin-dependent diabetics have decreased clearance [41]. Dysregulation may reduce the elimination rate alleviated by optimal insulin therapy. Patients with type II dia-

betes, which is difficult to control on oral antidiabetic drugs, are easier to control after induction of hepatic drug metabolism by phenobarbitone [41]. Congenital adrenal hyperplasia has no effect on antipyrine metabolism [22], nor has the administration of human growth hormone to children with growth retardation [42].

Various other diseases without obvious liver involvement may affect antipyrine kinetics. Heart failure [43] and pulmonary insufficiency are associated with a decreased elimination rate. Renal insufficiency does not impair the total clearance, although the metabolites are accumulated and the formation of norantipyrine may be decreased [11]. Pneumonia without gross disturbances of pulmonary function has been shown to reduce the antipyrine clearance by about one third [44]. Fever, experimentally induced in adults or related to respiratory tract infections in children, has a similar effect [45], presumably due to high interferon production.

In agreement with the previously mentioned importance of dietary protein content, pure energy malnutrition has no effect, whereas protein-calorie malnutrition inhibits antipyrine elimination [46]. Obesity and short-term fasting do not affect antipyrine kinetics [47].

Approximately 4 days after surgery lasting less than 2 h, the antipyrine clearance is increased, irrespective of the use of regional or general anaesthesia [14]. Surgery lasting for 4 h or more is usually followed by a reduced elimination rate [48].

Malignant diseases per se do not depress antipyrine metabolism. Equivalent elimination rates have been found in cancer-free controls and in patients with gastric cancer [49], leukaemia and hepatoma. On the other hand, increased elimination rates have been reported in patients with prostatic cancer, in primary hepatocellular carcinoma [26], in lung [50], and in testicular cancer [22]. Advanced malignant disease with secondary liver involvement and/or malnutrition is accompanied by depressed antipyrine elimination [49]. Considering the fact that many carcinogens require metabolic activation, signs of high microsomal enzyme activity in cancer patients may be indicative of involvement in carcinogenesis. In

TABLE 1  
CHANGES IN METABOLITE FORMATION RELATIVE TO THE TOTAL ANTIPYRINE CLEARANCE (APC)

Drug	APC	NORA	HMA	OHA	Ref.
Metronidazole	→	→	→	↓	52
Cimetidine	↓	→	→	→	15
Verapamil	↓	→	→	→	53
Diltiazem	↓	→	→	→	54
Oral					
contraceptives	↓	→	→	→	30
Alaproclate	↓	→	→	→	55
Primaquine	↓	→	→	→	56
Chloroquine	→	→	→	→	56
Phenobarbital	↑	↑	→	→	8
Antipyrine	↑	↑	→	→	8
Sulphinpyrazone	↑	↑	→	→	57
Rifapentine	↑	↑	→	→	58
Rifampicin	↑	↑	→	→	22
Spiroolactone	↑	↓	→	↑	59
Phenytoin	↑	→	↑	↑	60
Carbamazepine	↑	→	↑	↑	60

<sup>a</sup> Not investigated.

Abbreviations: NORA = norantipyrine; HMA = 3-hydroxymethylantipyrine; OHA = 4-hydroxyantipyrine.

fact, the half-life of antipyrine and the 3-methylcholanthrene induction of the enzyme, allegedly activating benzopyrenes into carcinogens in mitogen-stimulated cultured lymphocytes, correlated strongly in environmentally unperturbed subjects [51].

#### Interaction between antipyrine and other drugs

The pharmacokinetics of antipyrine are influenced by a large number of drugs. Antipyrine is probably the most widely used probe for the study of the effect of old and new drugs on hepatic drug metabolism. The results of the many studies published in the 1970s have been thoroughly reviewed by Vesell. Since then, some new and a few old drugs affecting antipyrine metabolism have been added to the list. One of

the most important is cimetidine. Many recent studies include the formation rates of the major antipyrine metabolites (Table 1). The inhibitors so far investigated in man, cimetidine, verapamil, diltiazem, oral contraceptives, primaquine, and alaproclate, have been shown not to cause differential effects. The inducers, antipyrine, rifampicin, rifapentine, phenobarbitone, sulphinpyrazone, spironolactone, phenytoin and carbamazepine, appear to have differential effects on antipyrine metabolism, i.e., the rate of formation of one metabolite is greater than that of others. This supports the hypothesis that there are at least three distinct cytochrome *P*-450 enzymes involved and stresses the importance of including metabolite measurement in future studies.

Studies on combined inducer-inhibitor effects are sparse, but the few which have been published indicate that the effects are additive [61,62].

#### Antipyrine in the future

The genetic influence on drug-metabolizing capacity is an expanding area where antipyrine has its place along with other model drugs like sparteine, debrisoquine, theophylline and hydralazine. A vast area where antipyrine, also in the future, may prove a valuable tool is the determination of the influence of exercise and environment. Some of these factors (gross differences in diet are known to have an influence on the drug-metabolizing enzymes) may very well exert differential effects on *P*-450 isoenzymes. Further studies on the influence of diseases, diet, drugs and environmental xenobiotics on the activation of drugs and chemicals to mutagens and carcinogens are called for in a world where an increasing number of substances are released into man's environment.

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