

KINETICS AND METABOLISM OF PYRAZOLONES (PROPYPHENAZONE, AMINOPYRINE AND DIPYRONE)

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- 1 Propyphenazone 220 mg was administered orally to volunteers. Maximum plasma concentrations between 1.5 $\mu\text{g}/\text{ml}$ and 3.5 $\mu\text{g}/\text{ml}$ were found 30 min later. After comparable doses plasma concentrations in dog and rabbit were lower. The distribution volumes were 2 l/kg.
- 2 The major metabolic route of propyphenazone is demethylation. The main urinary metabolite is the enolglucuronide of N-(2)-demethylpropyphenazone.
- 3 Aminopyrine is rapidly and almost completely absorbed after oral administration. Maximum plasma concentrations of 10 $\mu\text{g}/\text{ml}$ are reached 1.5 h after a 500 mg dose. The biological half-life is 2–3 h, the relative distribution volume 60% on average, and binding to plasma proteins approximately 15%.
- 4 Unchanged aminopyrine is only excreted in small quantities. The major routes of metabolism are demethylation (4-methylaminoantipyrene and 4-aminoantipyrene) and acylation (4-acetyl and 4-formylaminoantipyrene). There are other biotransformation products.
- 5 After oral administration of [^{14}C]-dipyron 480 mg the maximum serum concentration of 13.4 \pm 0.8 $\mu\text{g}/\text{ml}$ occurred at 1–1.5 hours.
- 6 Dipyron was not detectable in serum or urine. Four of seven metabolites were identified, and were identical with the main metabolites of aminopyrine.

Introduction

THE pyrazolones are among the oldest synthetic pharmaceuticals. Knorr first prepared antipyrene in 1883. Figure 1 represents the basic structure from which other pharmacologically important pyrazolones are derived by substitution on the C-4 atom.

In the search for derivatives with a greater therapeutic activity the hydrogen on C-4 of antipyrene was first substituted by the isopropyl radical to give propyphenazone. This has improved antipyretic and analgesic properties and exhibits anti-inflammatory activity.

Propyphenazone

There are few published reports about the plasma concentrations of propyphenazone after oral administration. Table 1 is a compilation of available pharmacokinetic data and it is clearly incomplete.

Sioufi & Marfil (1978) described a gas chromatographic method for the determination of propyphenazone. After oral administration of 220 mg a maximum of 1.6 $\mu\text{g}/\text{ml}$ approximately 1.2 h later was found. The limit of detection for this method is 125 ng/ml.

Using this method, maximum propyphenazone concentrations of 1.5–3.5 $\mu\text{g}/\text{ml}$ can be expected in the plasma after an oral dose of 220 mg and maximum concentrations of 3.5–12.5 $\mu\text{g}/\text{ml}$ after 440 mg. The maximum levels were reached 0.5–0.6 h after dosing (Ciba Geigy AG, 1979, unpublished data).

Dell & Kolle (1978) reported a thin layer chromatographic method, by which they were able to detect propyphenazone in the blood up to 10 h after an oral dose of 240 mg in man.

After propyphenazone (150 mg/kg orally) in rabbits (Figure 2), a maximum of 42 $\mu\text{g}/\text{ml}$ has been found (Naito, 1963) 2 h after administration with a mean biological half-life of approximately 2.8 \pm 0.6 h.

In dog (Dell *et al.*, 1978) and in rabbit (Naito, 1963) the given distribution volume is 2 l/kg.

The biotransformation of propyphenazone (Figure 3) has been investigated only in the rat (Tateishi & Shimizu, 1976) and in man (Tateishi & Shimizu, 1976; Ehrental, Pflieger & Pflieger, 1979). The major route of metabolism in both species is demethylation on the N-2 atom. The enol-glucuronide of N-2-demethylpropyphenazone is the main metabolite, accounting for about 80% of all the metabolites of

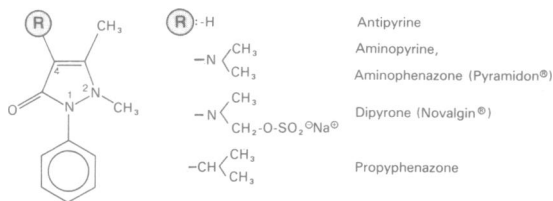


Figure 1 C-4-substituted antipyridines (= 2,3-Dimethyl-1-phenyl-pyrazoline-5-ones).

propyphenazone eliminated in urine. In addition various hydroxylation products occur in smaller quantities, partly free and partly conjugated.

Stolz in 1896 substituted the isopropyl radical of propyphenazone with a dimethylamino group (Figure 1) to obtain aminopyrine (aminophenazone). It was more toxic than antipyrine, but possessed greater antipyretic and analgesic activity. In addition it had marked anti-inflammatory and spasmolytic properties, and was marketed under the name Pyramidon® in 1897.

There are many reports on the kinetics and metabolism of amidopyrine in man.

Aminopyrine

Extensive pharmacokinetic studies of aminopyrine and its metabolites 4-acetylaminoantipyrine and 4-aminoantipyrine have been carried out by Koizumi, Ueda & Takada (1974).

After oral administration, aminopyrine is absorbed rapidly and almost completely. On average less than 2% of the dose appears in the faeces (Brodie & Axelrod, 1950). The maximum plasma concentration after a single oral dose (Table 2) is usually reached after 1.5 hours. Between 2.7 and 38 µg/ml were found, depending on the dose. In the dose range 150 to 850 mg the plasma half-lives were 2.1–3.2 hours. The half-lives in saliva were virtually identical to those in the plasma (Vesell, Passananti, Glenwright & Dvorchik, 1975).

There were no differences between children and young adults. Windorfer, Müller & Stehr (1977) found a serum half-life of 2.79±0.53 h in 2 to 11-yr-

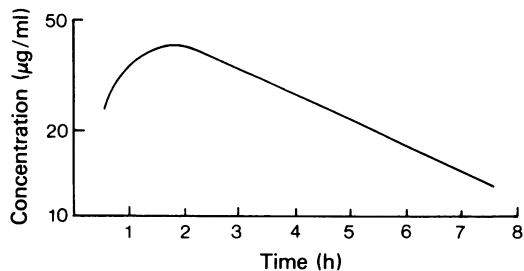


Figure 2 Plasma concentrations of propyphenazone in rabbits following an oral dose of 150 mg/kg. $t_{1/2}$ = 2.8 ± 0.6 hours. (Values taken from Naito, 1963.)

olds. In elderly people aged 65–86 yr, however, the plasma concentrations fell approximately five times slower than in the 25–30 yr age group (Jori, Di Salle & Quadri, 1972).

An increase in the half-life must also be expected in liver disease. In children suffering from hepatitis it was significantly increased to 6.71±3.34 h (Windorfer, Müller & Stehr, 1977). In uraemic patients, in contrast, there was no change in plasma concentrations and half-life compared with healthy volunteers (Leber, Harders & Schutterle, 1972). No sex-specific differences were found (Jori *et al.*, 1972). There are indications that aminopyrine elimination kinetics are dose dependent. Phenobarbital may increase the elimination rate (Roots, Saalfraank & Hildebrandt, 1975).

The relative distribution volume is given as 60% of the body volume (Roots *et al.*, 1975). According to Brodie & Axelrod (1950), aminopyrine is fairly evenly distributed throughout body water, similarly to antipyrine. The fraction bound to plasma protein is 15%.

After rectal administration absorption is slower and rate and plasma concentrations are lower but more constant (Anania, Borroni & Catanese, 1976).

A scheme for the metabolism of aminopyrine is shown in Figure 4.

The most important reactions in man are: (1) demethylation at the 4-position of the pyrazolone ring with formation of 4-methylaminoantipyrine and

Table 1 Pharmacokinetic characteristics of propyphenazone after a single dose in animals and man

Author	Species	Route of administration	Dose (mg/kg)	Dose (mg)	C _{max} (µg/ml)	t _{max} (h)	t _{1/2} (h)
Dell <i>et al.</i> (1971)	Dog	Oral (blood)	16		?	?	
		i.v. (blood)	24		?	1.0–1.5	0.63
Naito (1963)	Rabbit	Oral (plasma)	150		42	2	2.8±0.6*
Dell <i>et al.</i> (1971)	Man	Oral (blood)		240	?	~3	?
Sioufi & Marfil (1978)		Oral (plasma)		220	1.6	1.2	?
Ciba Geigy AG (Basel)		Oral (plasma)		220	1.5–3.5	0.5–0.6	1.0–1.5
		Oral (plasma)		440	3.5–12.5		

* Derived from graph.

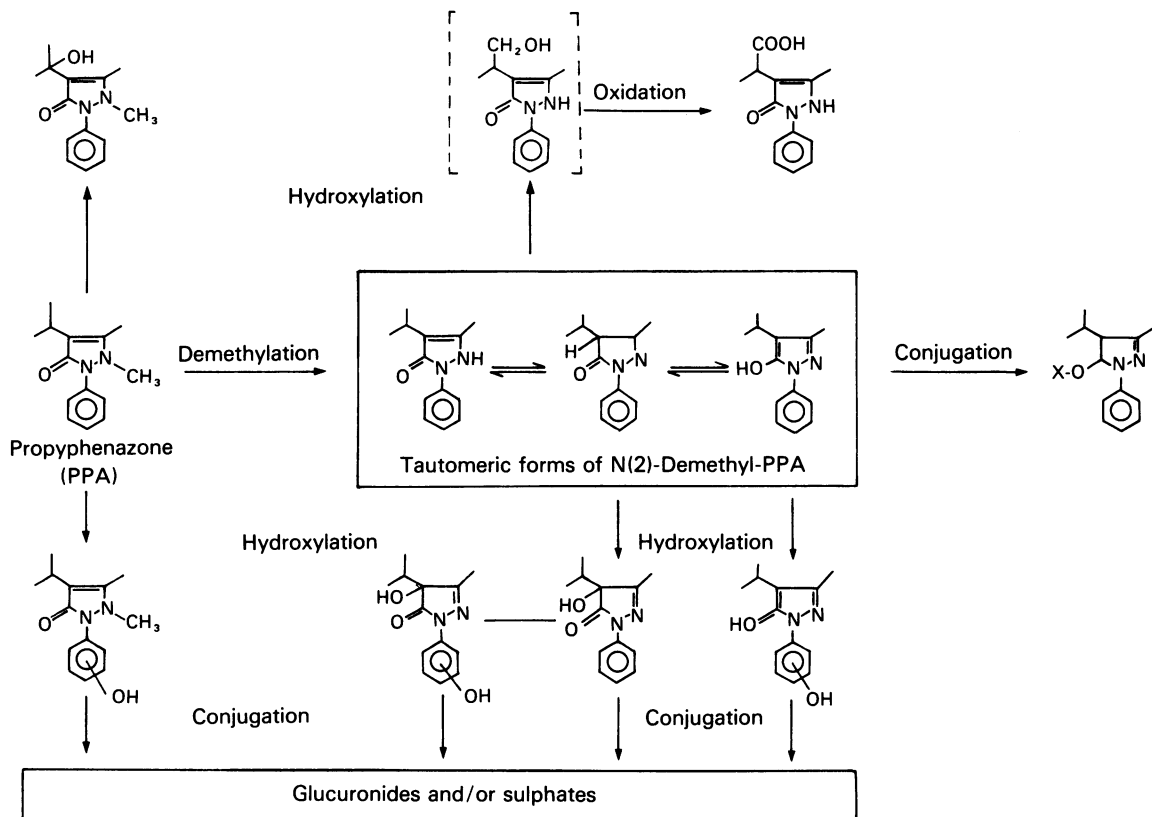


Figure 3 Metabolism of propyphenazone (PPA) in man. Dotted brackets, hypothetical intermediate; x; glucuronic and/or sulphuric acid. (Based on Tateishi & Shimizu (1976) and Ehrenthal *et al.* (1979).

Table 2 Pharmacokinetic characteristics of aminopyrine after a single oral dose in man

Author	Dose		C_{max} ($\mu\text{g/ml}$)	t_{max} (h)	$t_{1/2}$ (h)
	(mg/kg)	(mg)			
Vesell <i>et al.</i> (1975)	9	(~450)	6-12*	1.5	2.70±0.29
Jori <i>et al.</i> (1972)	(12)	600	17.4*	1.5	2.6*
Windorfer <i>et al.</i> (1977)	8-10	(400-500)	~ 10.0	1.5	2.90±0.64
	11-13	(500-650)	~ 16.0	1.5	2.50±0.30
	14-15	(700-750)	~ 26.0	1.5	3.20±0.55
	16-17	(800-850)	~ 38.0	1.5	2.80±0.60
	Anania <i>et al.</i> (1976)	(6)	300	10	0.5
Lavene <i>et al.</i> (1976)	(5)	250	2.7±0.43	1.6±0.2	2.3
Roots <i>et al.</i> (1975)	(12)	600	?	?	2.05
	(24)	1200	?	?	3.70±1.74

*Derived from graph.

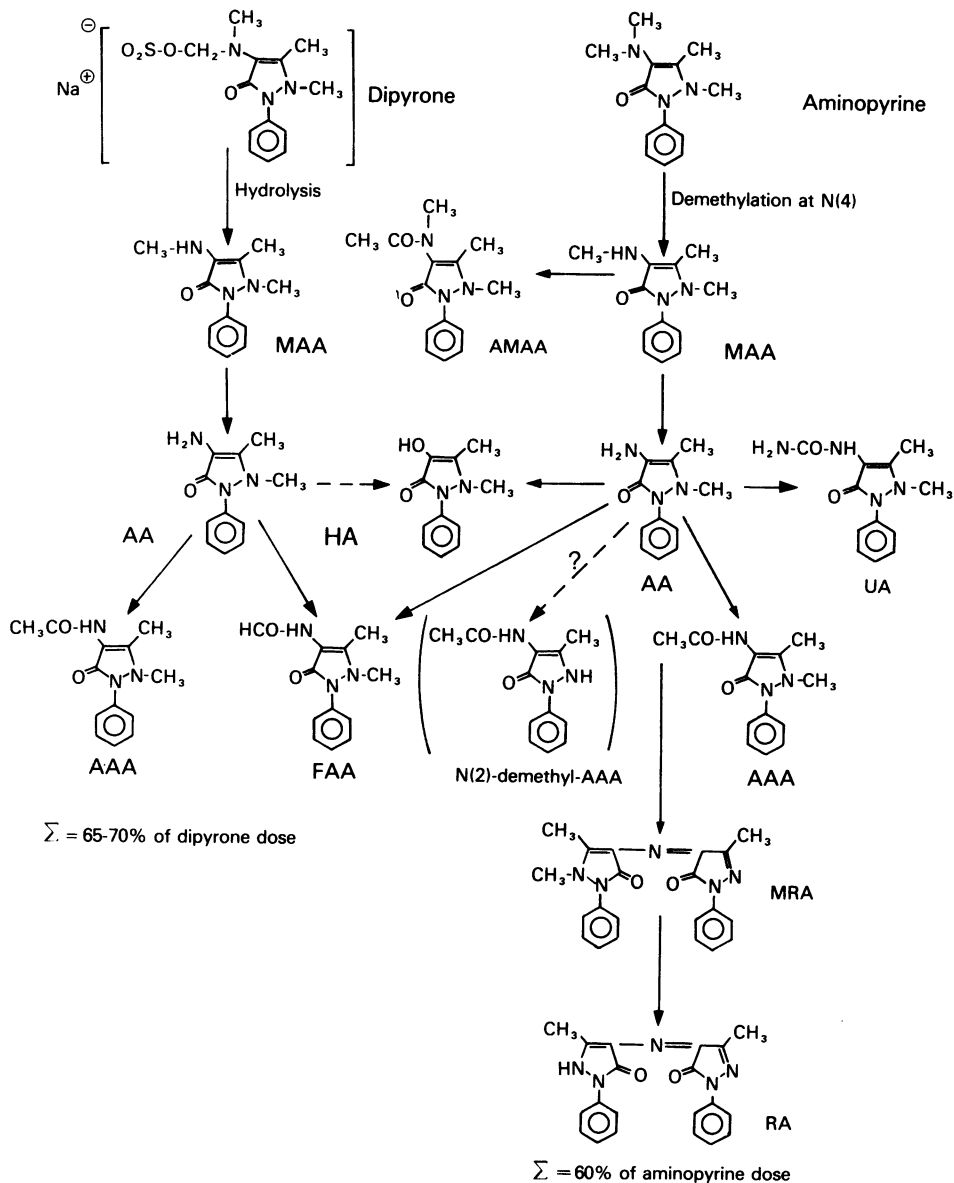


Figure 4 Comparison of the metabolism of dipyrone and aminopyrine in man, based on published and reported studies. MAA, 4-methylaminoantipyrine; AA, 4-aminoantipyrine; AAA, 4-acetylaminoantipyrine; FAA, 4-formylaminoantipyrine; HA, 4-hydroxyantipyrine; AMAA, 4-acetylmethylaminoantipyrine; UA, 4-ureidoantipyrine; MRA, methyl rubazonic acid; RA, rubazonic acid.

4-aminoantipyrine (Brodie & Axelrod, 1950; Halberkann & Fretwurst, 1950; Schüppel & Soehring, 1965; Pechthold, 1964a); and (2) acylation of these compounds to 4-acetylaminoantipyrine (Brodie & Axelrod, 1950; Halberkann & Fretwurst, 1950) and 4-formylaminoantipyrine (Iguchi, Goromaru & Noda, 1975).

The renal excretion of the known aminopyrine

metabolites is shown in Table 3. Aminopyrine is excreted unchanged in the urine only in small amounts up to 10% both after oral and rectal administration (Anania *et al.*, 1976).

The dominant metabolite, in urine, is acetylaminoantipyrine, accounting for 20–48% of the administered dose. It is eliminated with a biological half-life of approximately 8 h (7.8 ± 0.35 h) (Vessell *et al.*, 1975).

Table 3 Renal excretion of aminopyrine and its known metabolites after oral and rectal administration in man

Author	Aminopyrine	MAA	AA	AAA	FAA	MRA	RA	HA
<i>Oral administration (% dose)</i>								
Halberkann & Fretwurst (1950)	—	—	22.8	28.9	—	—	—	—
Brodie & Axelrod (1950)	3.2±1	—	8.3±3.4	35.8±8.9	—	—	—	—
Oehne & Schmid (1972)	3	3	8	48	—	—	—	—
Fleischman (1973)	1.36	3.74	4.47	23.67	—	2.67	0.23	0.34
Iguchi <i>et al.</i> (1975)	—	—	—	—	20	—	—	—
Lavedne <i>et al.</i> (1976)	0.73±0.26	—	6.49±0.63	23.96±2.27	—	—	—	—
Anania <i>et al.</i> (1976)	10	—	—	24	—	—	—	—
<i>Rectal administration (% dose)</i>								
Fleischmann (1973)	1.25	2.93	4.27	19.62	—	2.97	0.25	0.21
Anania <i>et al.</i> (1976)	8	—	—	20	—	—	—	—

MAA, 4-Methylaminoantipyrine; AA, 4-aminoantipyrine; AAA, 4-acetylaminoantipyrine; FAA, 4-formylaminoantipyrine; MRA, methylrubazonic acid; RA, rubazonic acid; HA, 4-hydroxyantipyrine.

Quantities of 4-aminoantipyrine (4–8% of the dose) in the urine are usually reported. In one case 23% was found (Halberkann & Fretwurst, 1950). The excretion of both substances, extends over 4–5 days. Only 3–4% of the administered dose appears in the form of 4-methylaminoantipyrine. On the other hand, the share of 4-formylaminoantipyrine accounts for up to 20%.

Quantitatively less important metabolites include 4-acetylmethylaminoantipyrine (Vecerkova, Kakac, Vecerek & Ledvina, 1967), 4-hydroxyantipyrine (Brodie & Axelrod, 1950; Halberkann & Fretwurst, 1950; Gradnik & Fleischmann, 1973), predominantly excreted conjugated with glucuronide or sulphate, and also rubazonic and methylrubazonic acid (Jaffe, 1901; Schüppel & Soehring, 1965; Pechtold, 1964*b*; Preuss & Voigt, 1965). The latter occur only sporadically and it has not been finally clarified whether they are artefacts or true metabolites of aminopyrine.

A further possible but unconfirmed biotransformation product of aminopyrine, namely, ureidoantipyrine, has been described by Jaffe (1902).

In 1970, Klug believed he had detected a new metabolite of aminopyrine. The substance he isolated, shown on the left of Figure 5, was thought to be identical with 4-acetylaminoantipyrine demethylated on the N-2 atom of the pyrazolone ring. However, our investigations suggest that it is 4-formylaminoantipyrine, an isomer; its R_F -values in various solvent systems and its molar composition, are identical with those of 4-formylaminoantipyrine, which we had detected in connection with dipyrone, but not with the synthetically produced reference substance of the metabolite postulated by Klug (1970).

The metabolites of aminopyrine detected in man are also found in other species. The following have been investigated: rat (Schüppel & Soehring, 1965;

Klinger, 1969; Yoshimura, Shimeno & Tsukamoto, 1970; Niwa, Hikichi & Sasaki, 1975) dog (Halberkann & Fretwurst, 1950; Pechthold, 1964*a*; Schüppel & Soehring, 1965) and rabbit (Yoshimura *et al.*, 1970; Niwa *et al.*, 1975). Although rat and rabbit are similar to man — 4-aminoantipyrine and its 4-acetyl- and formyl-derivative are the main metabolites — the dog behaves quite differently. Only small quantities of 4-acetylaminoantipyrine (0–5%) occur in the urine. The chief products (approximately 89%) are the original substance and 4-aminoantipyrine (10%) (Halberkann & Fretwurst, 1950).

Yoshimura *et al.* (1970) have reported three further minor aminoantipyrine metabolites in rats and rabbits (Figure 6) which are formed by oxidation of the methyl group on the C-3 atom. The aldehyde metabolite is particularly noteworthy. It can react with amino groups, forming Schiff bases. Niwa *et al.* (1975) have found a condensation product of 4-aminoantipyrine in the urine of rats and rabbits. By *in vitro* incubation with bovine gammaglobulin Shimeno & Yoshimura (1972) prepared a conjugate of this metabolite which led to the formation of antibodies against this metabolite when injected into rabbits. This is possibly a biochemical explanation of the pyrazolone allergy that is occasionally observed in man.

Recent investigations have shown that the dimethylamino group is very reactive and with nitrite or nitrogen oxides it is split off with formation of dimethylnitrosamine (Eisenbrand, Spiegelhalter, Kann, Klein & Preussman, 1979).

A disadvantage of aminopyrine is its relative insolubility in water (see above), and a compound was sought which was more water-soluble with all the pharmacological properties of aminopyrine. Such a compound, dipyrone, the sodium salt of antipyrinyl-methylamino-methanesulphonic acid was marketed under the name Novalgin® in 1922.

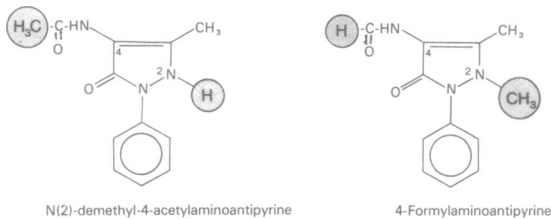


Figure 5 Isomerism between N-2-demethyl-4-acetylaminoantipyrine and 4-formylaminoantipyrine.

Dipyron

In contrast to aminopyrine, little is known of the kinetics and metabolism of dipyron. The following data are based mainly on our studies which have only been published in part.

After oral administration of [¹⁴C]-dipyron 480 mg in the form of three commercially available Novalgin® products, absorption is rapid and uniform. Figure 7 shows the curve of the total radioactivity in serum (Christ, Kellner, Ross, Rupp & Schwarz, 1973). In the upper right of the graph there is a detailed enlargement of the initial phase. The maximum concentrations (Table 4) were measured in man after 1–1.5 h (13.4±0.8 µg/ml). For comparison data in the rat and dog are given.

Dipyron itself is not detectable in the serum. Instead, at least seven metabolites occur, of which four can be identified. They are as follows (Table 5): 4-methylaminoantipyrine, 4-aminoantipyrine, 4-acetylaminoantipyrine and 4-formylaminoantipyrine;

4-Formylaminoantipyrine was discovered by us for the first time in 1973 as one of the chief metabolites of dipyron in the serum and urine of man. Iguchi *et*

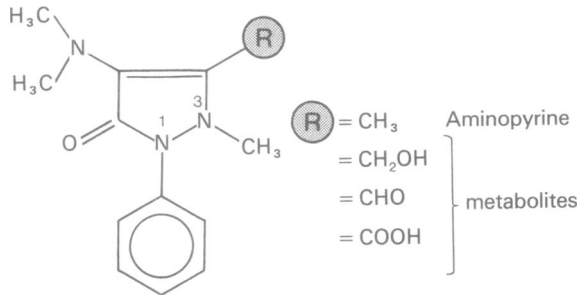


Figure 6 Oxidation products of aminopyrine at C-3.

al. (1975) have also described this substance as a metabolite of aminopyrine.

Initially the metabolite occurring in the highest concentrations is 4-methylaminoantipyrine. This result is in agreement with those of other researchers (Weiss, Brauer, Goertz & Petry, 1974). The maximum plasma concentration (Figure 8), occurs as early as 1 h after oral and intramuscular administration. However, after intramuscular administration the maximum concentration is significantly higher; there are no other differences in the kinetic properties. According to Weiss *et al.* (1974) the biological half-life is 2.4 h, 4-aminoantipyrine reaches a maximum 4 h after administration (see Figure 8). According to Weiss *et al.* (1974) the half-life for elimination in the plasma is 3.8 h after oral administration. After intramuscular injection the half-life is only 2.1 hours.

Whereas 4-methylaminoantipyrine and 4-aminoantipyrine are hardly detectable in the plasma 24 h after administration the concentration of 4-acetylaminoantipyrine after oral administration is still

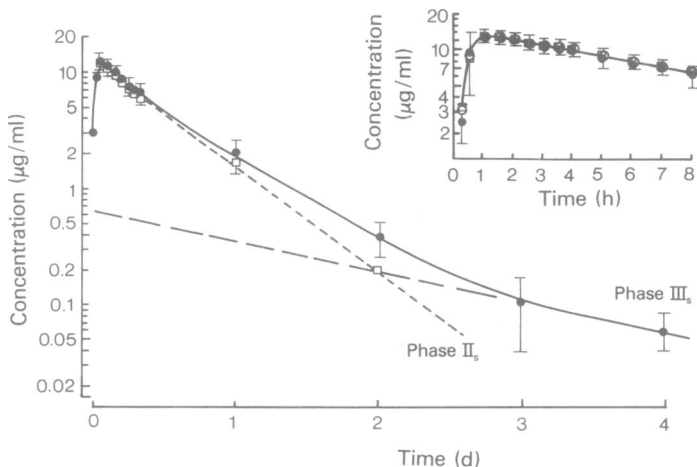


Figure 7 Serum levels after oral administration of [¹⁴C]-Novalgin® 480 mg ([¹⁴C]-dipyron 480 mg) as three different tablet types to man ($X \pm s.d.$) ●, A ($n = 5$); □, B ($n = 6$); ○, C ($n = 6$).

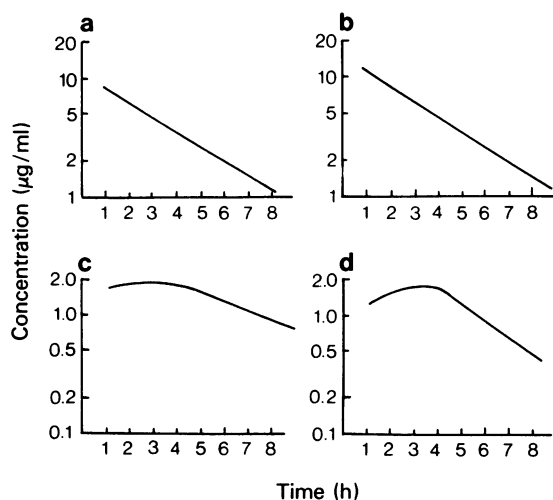


Figure 8 Time course of 4-methylaminopyrine (*a* and *b*) and 4-aminoantipyrene (*c* and *d*) in human plasma after oral administration of dipyrone 1000 mg. *a* and *c*, orally; *b* and *d*, intramuscularly (Weiss *et al.*, 1974).

about one-half the maximum concentration at this time.

Two hours after administration, the plasma level of formylaminoantipyrene is 2.5 ± 0.8 µg/ml. At 2–8 h the biological half-life is 9.9 ± 2.9 h (Table 5). The concentrations of two of the unidentified three metabolites are of the order of magnitude of 4-aminoantipyrene. The third metabolite only accounts for 2–5% of the maximum total concentration in the plasma.

Six metabolites of dipyrone are detectable in the urine after oral administration. Four are identical to those in the plasma. Their mean concentrations in urine are shown in Table 6. The unidentified remainder consists of at least two metabolites, including conjugated 4-hydroxyantipyrene, presumably a glucuronide. However, this metabolite has not yet been clearly identified.

As can be conjectured from their close chemical relationship, the biotransformation of dipyrone is virtually identical to that of aminopyrine. However, this does not apply to the formation of dimethylnitrosamine (Eisenbrand *et al.*, 1979).

We have compared the identified metabolites of

Table 4 Pharmacokinetic characteristics of dipyrone in plasma or serum calculated from ^{14}C -radioactivity after a single dose of [^{14}C]-novalgin ([^{14}C]-dipyrone) to animals and man (Christ *et al.*, 1973)

Species	Route of administration	Dose (mg/kg)	n	C_{\max} (µg/ml)		t_{\max} (h)	$T_{1/2}$ (h)	
				Blood	Serum		Phase II _{B,S}	Phase III _{B,S}
Rat	Intravenous	50	5				2.7	—
	Oral	46	5	23 ± 2		2	2.4	≈ 230
Dog	Intravenous	50	3				5.2 ± 1.0	92 ± 22
	Oral	50	3	40 ± 3		1.5–2	4.4 ± 0.5	146 ± 41
	Rectal	85	3	20 ± 6		2–4	5.4 ± 0.5	158 ± 11
Man	Oral	5.8 ± 0.7	6		13.4 ± 0.8	1.0–1.5	6.9 ± 0.9	—

Table 5 Pharmacokinetic of the metabolites of dipyrone in plasma or serum after oral administration to man

Author	Metabolites of dipyrone	Dose of dipyrone (mg)	C_{\max} (µg/ml)	t_{\max} (h)	$t_{1/2}$ (h)
Christ <i>et al.</i> (1973)	Total radioactivity	480	13.4 ± 0.8	1–1.5	6.9 ± 0.9
Weiss <i>et al.</i> (1974)	4-Methylaminoantipyrene	1000	7.8 ± 2.1	1	$2.4 \ddagger$
Ebner (1977)		400	2.7	1–2	?
Volz (unpublished)		480	$4.2 \pm 1.6^*$	2	ND
Weiss <i>et al.</i> (1974)	4-Aminoantipyrene	400	1.7 ± 0.5	4	$3.8 \S$
Volz (unpublished)		480	1.4 ± 0.3	4	ND
Weiss <i>et al.</i> (1974)	4-Acetylaminoantipyrene	400	$0.8 \pm 0.6 \dagger$	8	?
Volz (unpublished)		480	$1.7 \pm 0.8^*$	8	ND
Volz (unpublished)	4-Formylaminoantipyrene	480	$2.5 \pm 0.2^*$	2	9.9 ± 2.9

* First time of evaluation; maximum levels at an earlier time were possible.

† According to time course higher levels at later times are possible.

‡ Value after intramuscular and oral administration.

§ About 2.1 h after intramuscular injection.

ND, Not determined.

Table 6 Biotransformation products in human urine after a single dose of [¹⁴C]-dipyron 480 mg

Time (hrs)	Total radioactivity (% dose)	n	4-Formylamino antipyrine	4-Acetylamino antipyrine	4-Amino antipyrine	4-Methylamino antipyrine	Unidentified metabolites
0-24	71±6	6	23±5%	30±5%	6±3%	7±4%	32±7%
24-48	18±7		30±4%	50±4%	4±2%	~1%	17±2%

both substances in Figure 4. On the left are shown the known metabolites of dipyron. Only the formation of 4-methylaminopyrine takes a different course for both substances, in the case of aminopyrine by demethylation; and in the case of dipyron by hydrolysis.

Dipyron is metabolized by the rat in a similar way to man (Nogami, Hamano, Awazu & Imaoka, 1970). As with aminopyrine, the dog deviates from this pattern (Volz, unpublished data).

The metabolites of aminopyrine which have been identified constitute only about 60% of the administered dose and 65-70% of a dose of dipyron. In the

case of dipyron, we know that not all metabolites have been identified. This could also apply to aminopyrine. But there may be a different explanation. Zietz, Eichelbaum, Dengler & Spittler (1978) have shown that the apparent deficit of [¹⁴C]-labelled antipyrine, does not exist at all, but is attributable to inadequate methods of analysis and/or decomposition of the metabolites.

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In response to a question from Professor Ghaleb, Dr Prescott emphasized that the relatively high proportion of glucuronide seen was due to depression of sulphate conjugation and to the delayed appearance of other metabolites. Cysteine and mercapturic acid conjugates took a long time to reach peak production, or peak appearance in urine. The high amount of glucuronide reflected the diminished proportion of other metabolites. Where there was substantial overdose, there was almost complete inhibition of sulphate production within 1-2 h of ingestion of the dose. There was no time for induction or other changes in enzyme activity in this period.

Professor Ghaleb said that his question referred to exposure to drugs or environmental influences causing induction before exposure to paracetamol, and their effect on its metabolism.

DR MITCHELL reported that volunteers exposed to paracetamol before and subsequent to exposure to

phenobarbitone showed a minimal increase in glucuronidation, and thought that the increase shown by Dr Prescott was indeed due to saturation of the sulphation pathways. He said it was only possible to determine whether glucuronidation or other pathways were saturated at doses in which all processes were first order, that is, not huge overdoses, Dr Mitchell asked whether radiolabelled N-acetylcysteine, cysteine or cysteamine in tracer amounts had been administered to overdose patients.

DR PRESCOTT replied that he had not done so, but that comprehensive studies on the urinary excretion of the metabolites in tested patients showed that if N-acetylcysteine was given there were increased amounts of paracetamol sulphate, cysteine and mercapturic acid. This implied that N-acetylcysteine acted either as a direct substrate for conjugation or as a supplier of cysteine for glutathione synthesis and eventual conjugation.

DR MITCHELL asked whether patients who received high doses of paracetamol but did not show liver injury also excreted only 4% each of the two cysteine-acetylcysteine conjugates.

DR PRESCOTT replied that where there were high but not hepatotoxic doses, the amount of sulphate conjugation seemed to be less. The amounts of cysteine and mercapturic acid, as a proportion of the total recovered, were about the same as those found in volunteers given low therapeutic doses.

DR WÜRZ asked in what range the lethal dose of paracetamol for children and adults lay.

DR PRESCOTT replied that there was some evidence that children were less sensitive to the hepatotoxic effects of paracetamol, and that although many children were reported to have taken paracetamol accidentally few were reported to suffer liver damage. It was possible that they were not less sensitive but that they took smaller amounts. Studies of plasma levels of paracetamol have shown few in the toxic range. However, in practical terms children were less likely to develop liver damage.

Regarding lethal doses, Dr Prescott said there was substantial variation. Some groups were particularly at risk, for example, chronic alcoholics, perhaps

because they had enzyme induction which accelerated the formation of toxic metabolites, or perhaps because they could not make glutathione. If 30 g or 40 g were taken there would be a substantial risk; on the other hand, it was possible to take this dose and not to die. It was also possible to take perhaps only 10 g or 15 g and to suffer severe liver damage. He emphasized that patients could give totally unreliable information about the quantity of drug they had taken.

DR G. LEVY pointed out that there was considerable information available about aspirin taken in large doses for long periods, but very little about paracetamol taken in the same way. Moreover, the toxic effect of paracetamol was due to a reactive metabolite, the formation and concentration of which was a function of all the processes involved in its elimination — primarily sulphate formation and glucuronidation, as well as the rate constant of the formation of the reactive metabolite. There were, he said, at least four and perhaps as many as six rate constants. In a large population it would be possible to find a combination of these rate constants such that paracetamol 4, 5 or 6 g daily would be sufficient to cause hepatotoxicity. He pointed out that this was hypothetical at present but realistic in pharmacokinetic terms.