J. Pharm. Pharmacol. 1982, 34: 744–746
Communicated March 23, 1982

0022–3573/82/110744–03 $02.50/0

Modification of methaqualone pharmacokinetics by diphenhydramine

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The sedative-hypnotic and anticonvulsant properties of methaqualone, discovered in our laboratory (Gujral et al 1955, 1957), have in recent years been greatly abused (Temant 1973; Pascarelli 1973). The drug also produces a state of tolerance to other drugs as well as to its own response (Prabhu et al 1967; Ballinger et al 1972; Brown & Goenechea 1973) and a combination (250:25 mg) with diphenhydramine (Mandrax) has been shown to be a better sedative than either of its constituents or a placebo alone (Norris & Telfer 1969; Brown & Goenechea 1973).

Methaqualone is completely absorbed from intestine and metabolized by non-specific cytochrome P-450 dependent microsomal mixed function oxidases (MFO) to hydroxylated metabolites which are eliminated as glucuronide conjugates (Preuss et al 1966; Nowak et al 1966). Diphenhydramine is also metabolized by the microsomal enzyme system to yield *N*-oxide, demethylated and deaminated metabolites which are ultimately excreted as glutamine and glycine conjugates (Drach et al 1970). It is possible that the interaction of these two drugs at the level of their biotransformation results in the altered response to methaqualone. Little is understood about the possible pharmacokinetic interaction between the two drugs and its implication in the potentiation of methaqualone response. We have previously reported differential stimulation of the metabolism of drugs in rats given long-term intraperitoneal (Parmar et al 1974) and oral (Ali et al 1980) methaqualone treatment.

We have now examined the possible alteration in the pharmacokinetics of methaqualone that may occur on administration of diphenhydramine in rat.

Materials and methods

Male Albino rats, 125–175 g, with free access to food and water were treated intraperitoneally for 20 days with diphenhydramine (12 mg kg^{-1} day^{-1}) in 0·9% NaCl (saline). 14–16 h after the last dose of diphenydramine the rats were given methaqualone (60 mg kg^{-1} i.p.) in saline, pH 3–4. At different intervals from the time of methaqualone administration, blood samples from animals were collected in heparinized tubes directly from the heart, using a heparinized syringe and mild anaesthesia induced with chloroform and the plasma concentration of methaqualone was measured.

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To evaluate the influence of a single concurrent dose of diphenhydramine on the disposition of methaqualone in rats a combined dose comprised of methaqualone 60 mg kg^{-1} and diphenhydramine 12 mg kg^{-1} in saline, pH 3–4 was administered intraperitoneally. Controls received the same amount of saline, pH 3–4. Blood samples were collected directly from heart at intervals from the time of drug administration and serial plasma concentrations of methaqualone measured.

Estimation of methaqualone

The spectrophotometric method (Seth et al 1977) was modified to estimate methaqualone in plasma. Plasma was separated out by centrifuging the blood at 1000 *g* for 30 min and analysed for methaqualone concentration. Plasma (1 ml) was made alkaline with 0·5 ml of 0·1 M NaOH and shaken vigorously with chloroform (10 ml) for 30 min. The organic phase was separated from the aqueous one and evaporated to dryness on a boiling water bath. The residue thus obtained was taken into 4 ml of 0·1M HCl and the acidic solution containing methaqualone was read at 232 nm.

Pharmacokinetic calculations

Pharmacokinetic parameters were calculated using the appropriate formulae applicable for a single open compartment model as described by Notari et al (1975). Area under curve was calculated by the trapezoid rule.

Table 1. Effect of concomitant administration of diphenhydramine on methaqualone pharmacokinetics.

Pharmacokinetic profiles of methaqualone	Control*	Test*	Increase (+) or decrease (−) %
Biological half-life ($t_{1/2}$) h	2·32 ± 0·5	5·03 ± 0·6	116 (+) ($P < 0·02$)
Elimination rate constant (Ke) h^{-1}	0·298 ± 0·06	0·137 ± 0·009	54 (−) ($P < 0·05$)
Area under curve (AUC) $\mu g\ h^{-1}\ ml^{-1}$	120 ± 14	265 ± 28	120 (+) ($P < 0·01$)
Apparent volume of distribution (aVd) litre	0·231 ± 0·015	0·216 ± 0·025	6·5 (−) (NS)
Metabolic clearance rate (MCR) litre h^{-1}	0·068 ± 0·009	0·029 ± 0·002	57 (−) ($P < 0·01$)

* Values are mean ± s.e. of five rats. Diphenhydramine and methaqualone were given intraperitoneally. NS not significant.

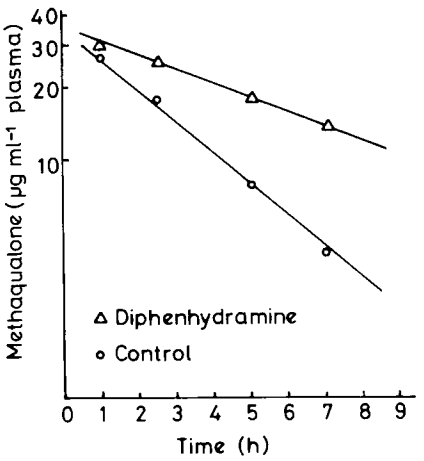

FIG. 1. Plasma concentrations of methaqualone (60 mg kg^{-1}) administered intraperitoneally alone (○——○) and concurrently with diphenhydramine (12 mg kg^{-1}) (△——△) in rat. Values are average mean for 5 animals.

The metabolic clearance rate was calculated using the standard formula MCR = aVd × 0·693/t ½ (Kappas et al 1976).

Methaqualone was obtained from Boots Co. (India) Ltd and diphenhydramine hydrochloride from Parke-Davis (India) Ltd. All other chemicals were of analytical grade.

Results and discussion

The present study was designed to elucidate the mechanism of interaction of diphenhydramine with methaqualone at the metabolic level which could possibly be responsible for the potentiation of the latter's response. In control animals methaqualone half-life was found to be 2·32 h (Table 1), which may be compared with the turnover of methaqualone in rat and mice after 100 mg kg^{-1} by mouth giving an average sleeping time of 104 and 77 min respectively (Prabhu et al 1964). This finding was further reflected by rapid clearance of the drug from plasma in mice (Seth et al 1977).

In the present study, diphenhydramine and methaqualone were administered intraperitoneally at 12 and 60 mg kg^{-1} (1:5) respectively. As is evident from Fig. 1, methaqualone pharmacokinetics were significantly altered when it was administered in combination with diphenhydramine. Diphenhydramine caused 54 and 57% decrease in the elimination rate constant and metabolic clearance rate respectively of methaqualone thus resulting in 116% increase in its biological half-life (Table 1). The apparent volume of distribution was not significantly affected whereas the area under curve was increased to 120% above the control values.

Chronic intraperitoneal treatment of animals with diphenhydramine alone (12 mg kg^{-1} day^{-1}) for 20 days was devoid of any effect on the metabolism of methaqualone administered in a single dose of 60 mg kg^{-1} 14–16 h after the last dose of diphenhydramine (Table 2). This could be because diphenhydramine disposition is rapid and therefore insufficient diphenhydramine would be still present to cause a significant alteration in methaqualone pharmacokinetics. Following its intravenous administration to rats, plasma levels of unchanged diphenhydramine were reported to fall with an estimated biological half-life of about 1 h (Drach et al 1970). The ineffectiveness of diphenhydramine as an inducer of microsomal MFO catalysing methaqualone metabolism in rat in the current study is clearly apparent from the results.

Table 2. Effect of chronic diphenhydramine administration on methaqualone pharmacokinetics.

Pharmacokinetic profiles of methaqualone	Control*	Test*	Increase** (+) or decrease (−) %
Biological half-life (t ½) h	2·32 ± 0·21	2·17– ± 0·2	6·5 (−)
Elimination rate constant (Ke) h^{-1}	0·298 ± 0·032	0·319 ± 0·033	7·0 (+)
Area under curve (AUC) μg h^{-1} ml^{-1}	122 ± 10	122 ± 11	Nil
Apparent volume of distribution (aVd) litre	0·224 ± 0·02	0·213 ± 0·019	4·9 (−)
Metabolic clearance rate (MCR) litre h^{-1}	0·066 ± 0·005	0·067 ± 0·006	1·5 (+)

* Values are mean ± s.e. of five rats. Methaqualone was administered intraperitoneally.
** *P*-Statistically insignificant.

The current study has shown that methaqualone disposition was reduced more than 2 fold in the rats given diphenhydramine at the same time as the hypnotic. It also suggests inhibition of microsomal MFO catalysed methaqualone biotransformation is caused by concomitant administration of diphenhydramine resulting in the potentiation of methaqualone response. This is supported by an earlier observation where diphenhydramine caused appreciable decrease in the rate of in vitro biotransformation of methaqualone to one of its major inactive metabolites 2-methyl-3-(2-hydroxymethylphenyl)-4-(3H)-quinazolone in the 10 000 *g* supernatant fraction from rat liver (Hindmarsh et al 1978). This inhibition of MFO catalysing methaqualone metabolism was competitive. Moreover, it has been reported earlier that methaqualone causes an inhibition of hepatic microsomal *N*-demethylation of diphenhydramine, pethidine, morphine and hydroxylation of aniline in vitro (Ali et al 1980). It is thus likely that the inhibition of diphenhydramine metabolism under such conditions may result in the elevation of its effective concentration available for modification of methaqualone pharmacokinetics thereby producing an additive effect.

Acknowledgement is due to the Council of Scientific and Industrial Research, New Delhi for providing

Senior Research Fellowship to Miss Krishna P. Gupta. We thank Dr A. Kumar for advice and encouragement. Thanks are due to Parke-Davis (India) Ltd for a gift of diphenhydramine hydrochloride.

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J. Pharm. Pharmacol. 1982, 34: 746–749
Communicated May 4, 1982

0022–3573/82/110746–04 $02.50/0

Parabolic structure-activity relationships: a simple pharmacokinetic model

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Several models have been proposed for the parabolic relationship that many drugs show between pharmacological response and lipophilicity. Hansch and coworkers (Penniston et al 1969; Hansch & Clayton 1973) have proposed that the parabolic relationship arises from the passive diffusion of the drug through alternating aqueous and lipid phases and produced computer simulations to substantiate this argument. McFarland (1970) also considered a system comprising alternating aqueous and lipid phases and using probability arguments derived a bilinear equation to describe the relationship between pharmacological response and lipophilicity. Kubinyi (1976, 1977) has extended McFarland's work and reported that the bilinear model explains most of the data in the literature better than Hansch's quadratic model.

Since an in vivo biological system is much more complicated than a series of alternating aqueous and lipid phases, these models must be viewed as empirical rather than fundamental. Consequently we will use the term 'parabolic' to describe the situation in which, amongst a group of compounds with varying lipophilicity one compound elicits the largest pharmacological response (per unit dose). The term is not meant to imply quadratic in the sense of Hansch.

All of the approaches that have been proposed so far have as their basis the postulate that pharmacological response is determined by the ability of the drug to reach its receptor site. While this postulate is undoubtedly correct, the contribution of the drug's pharmacokinetics to its concentration at the receptor site has been neglected. Thus all of the proposed models are closed in that the drug accumulates at the receptor site. It was the purpose of the present study to investigate, in the most elementary fashion, the impact of pharmacokinetics on structure-activity relationships.

Closed model

The simplest example of alternating aqueous and lipid phases consists of an aqueous-lipid-aqueous sequence as shown in Fig. 1. The aqueous to lipid rate constant is k_1 and the lipid to aqueous rate constant is k_2. Assuming that the volumes of the three compartments are equal, the rate equations governing the drug concentration in the three compartments are

$$\frac{dC_1}{dt} = -k_1C_1 + k_2C_2 \quad (1)$$

$$\frac{dC_2}{dt} = k_1C_1 - 2k_2C_2 + k_1C_3$$

$$\frac{dC_3}{dt} = k_2C_2 - k_1C_3$$

* Correspondence.