

# Extrapolating from animal studies to the efficacy in humans of a pretreatment combination against organophosphate poisoning

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**Abstract** The extrapolation from animal data to therapeutic effects in humans, a basic pharmacological issue, is especially critical in studies aimed to estimate the protective efficacy of drugs against nerve agent poisoning. Such efficacy can only be predicted by extrapolation of data from animal studies to humans. In pretreatment therapy against nerve agents, careful dose determination is even more crucial than in antidotal therapy, since excessive doses may lead to adverse effects or performance decrements. The common method of comparing dose per body weight, still used in some studies, may lead to erroneous extrapolation. A different approach is based on the comparison of plasma concentrations at steady state required to obtain a given pharmacodynamic endpoint. In the present study, this approach was applied to predict the prophylactic efficacy of the anticholinergic drug caramiphen in combination with pyridostigmine in man based on animal data. In two species of large animals, dogs and monkeys, similar plasma concentrations of caramiphen (in the range of 60–100 ng/ml) conferred adequate protection against exposure to a lethal-dose

of sarin (1.6–1.8 LD<sub>50</sub>). Pharmacokinetic studies at steady state were required to achieve the correlation between caramiphen plasma concentrations and therapeutic effects. Evaluation of total plasma clearance values was instrumental in establishing desirable plasma concentrations and minimizing the number of animals used in the study. Previous data in the literature for plasma levels of caramiphen that do not lead to overt side effects in humans (70–100 ng/ml) enabled extrapolation to expected human protection. The method can be applied to other drugs and other clinical situations, in which human studies are impossible due to ethical considerations. When similar dose response curves are obtained in at least two animal models, the extrapolation to expected therapeutic effects in humans might be considered more reliable.

**Keywords** Caramiphen · Clearance · Pharmacokinetics · Prophylaxis · Pyridostigmine · Steady state

## Introduction

Therapeutic treatment against organophosphate (OP) poisoning has been studied extensively since World War II. Nevertheless, the currently adopted treatments (such as those supplied by atropine-oxime autoinjectors) are not fully satisfactory under actual life-threatening conditions (Levy et al. 2000). Pretreatment with pyridostigmine improves the efficacy of these autoinjectors, but does not confer any protection by itself. In addition, the two main disadvantages of most current antidotal treatments are: (a) they have to be administered shortly following exposure, a

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requirement that is rarely feasible; (b) they do not block efficiently nerve-agent induced seizures (McDonough et al. 1999; Gilat et al. 2003). Unless treated promptly, these seizures may lead to severe and prolonged brain injury (Kadar et al. 1992, 1995; Petras 1994). Addition of anticonvulsive drugs to the atropine-oxime treatment regime is therefore highly recommended (e.g. diazepam or its pro-drug avizafone). Recent published studies (e.g. McDonough et al. 1999; Lallement et al. 1999; Gilat et al. 2003) pointed out towards other more effective anticonvulsive treatments, which might be implemented in the future.

The prophylactic approach was suggested in an attempt to overcome the two difficulties mentioned above. Such pretreatment combinations are expected to confer protection by themselves as well as allow an extended time interval for the antidotal treatment of casualties and protect against the ensuing seizures. Most of the prophylactic mixtures that have been studied over the last two decades (e.g. Harris et al. 1980; Leadbeater et al. 1985; Meshulam et al. 1995, 2001; Raveh et al. 1996, 1999, 2002) were composed of a reversible cholinesterase inhibitor (i.e. the carbamates pyridostigmine or physostigmine) and an anticholinergic drug (e.g. caramiphen, aprocphen or scopolamine). Prophylactic treatment is given, by definition, to healthy individuals before any assault had occurred. This is the source of the “pretreatment dilemma”. On the one hand, the desire to provide maximal protection dictates the use of drug doses as high as possible. On the other hand, to ensure minimal or no adverse effects, the use of doses as low as possible is preferred. To design a research that will resolve this issue, the pertinent question can be formulated both ways:

- (a) What dose is required to achieve in humans a desired protection (subsequently testing it for adverse effects), or otherwise,
- (b) What protection is conferred by the dose tolerated in humans?

One of the basic problems in pharmacological studies is the extrapolation from animal data to the expected effects in humans. In most cases, however, preclinical studies in animals are followed by clinical human studies that corroborate and fine-tune the data. The problem is especially critical in OP poisoning studies, since human toxicity and protection data are not readily available. While the dose of a prophylactic drug that has no adverse effects can be determined in human studies, its protective efficacy has to be estimated based on animal experiments only (e.g. see Levy et al. 1993).

Anticholinergic drugs, as many other drugs, exert their activity through binding to membrane-receptors on cells of their target organs. These receptors and their distribution in different mammals are not identical, but similar enough to allow similar response to the pertinent drug. Assuming this similarity, the anticholinergic effects will be mainly controlled by the drug concentration in contact with these receptors. One of the commonly accepted assumptions in pharmacology is the relation between drug effects and their concentrations at target organs. However, while executing animal studies we mostly sample and analyze drug concentrations in the blood. Drug concentrations at target organs equilibrate with the concentration in the blood only at steady state. Consequently, there might be a lag period between the distribution in the blood compared to that in the target organ. At steady state, measurements of drug concentrations in the plasma may represent better its concentrations at target organs and possibly correlate with their effects. The tolerated concentrations of various drugs in humans (i.e. the dose leading to no overt adverse effects) can be found in the literature (e.g. for caramiphen see Levandoski and Flanagan 1980). To test the correlation between the protective effect and plasma concentrations at steady state of anticholinergic drugs, prophylactic protection studies were carried out using the pretreatment combinations pyridostigmine—caramiphen in dogs and monkeys. The effective dose of pyridostigmine was extrapolated from animal studies to humans based mainly on the pharmacodynamic parameter of cholinesterase inhibition (Dunn and Sidell 1989; Marino et al. 1998; Layish et al. 2005). Thus, this study focused on extrapolating the protective dose of caramiphen. The pharmacokinetics and specifically the biotransformation of drugs, varies between species and even between individuals of the same species. These individual changes were also taken into account in the design of the present studies, whose aim was to enable the extrapolation from animal data to protective efficacy against OP poisoning in humans.

## Methods

Beagle dogs (male, 14–16 kg during the study) or Papiou anubis monkeys (male and female, 5–7 kg) were used in the various protection studies.

Caramiphen edisilate was purchased from Secifar, Italy. Pyridostigmine hydrobromide was purchased from Sigma Chemical Co., UK.

Sarin was supplied by the Organic Chemistry department of the IIBR. Freshly prepared sarin solu-

tions were administered intravenously (iv) ( $LD_{50}$  of 20  $\mu\text{g}/\text{kg}$  for both monkeys and dogs) at doses of 1.6–2.25  $LD_{50}$  (lethal doses with no treatment).

Alzet mini-osmotic pumps (2ML1 model 2001, Alza, Palo Alto, CA, USA) were used for drug delivery over 48 h. Rompun solution (Xylazine 2%) was used for anesthesia (Bayer, Leverkusen, Germany).

Intravenous infusion to conscious monkeys was carried out at a rate of 20–30 ml/h using a peristaltic pump (Minipuls 2, Gilson, France) that was calibrated precisely before each experiment. The exact concentration of caramiphen (in mg/ml) was determined according to the calibrated rate (in ml/h) and the required rate of caramiphen infusion (in mg/h).

The clinical status of the animals following exposure was evaluated according to a clinical rating scale for the severity of the poisoning symptoms (see Table 1). Higher score values indicate more severe poisoning symptoms. Scores of symptoms considered as most essential were assigned a weight factor of 3, scores of other symptoms were assigned a weight factor of 2. All the scores were summed up following two days of observation. The maximal severity score was 67, the score also given to animals that died. Severe symptoms related to convulsions, breathing and posture difficulties had four levels of severity (0–3) and contributed each nine points to the total score. A non-convulsing animal, with a score of 15 or lower, was considered to be in a satisfactory condition. A clinical score of 40 or above described an animal in a severe clinical condition.

For the determination of caramiphen, plasma samples were first extracted into cyclohexane under basic conditions, with arophen used as an internal standard. Caramiphen concentration was determined by a validated gas-chromatographic method, using HP-5 column and NP detector (modified from Levandoski and Flanagan 1980).

**Table 1** A clinical severity rating score for OP poisoning symptoms

The clinical symptom	Severity scores	Weighing factor	Total maximal score
Salivation	0–2	2	4
State of consciousness	0–2	3	6
Response to acoustic stimuli	0–2	2	4
Convulsions	0–3	3	9
Breathing	0–3	3	9
Posture	0–3	3	9
Coordination	0–3	2	6
Tonus	0–2	2	4
General condition at 6 h	0–2	2	4
General condition at 24 h	0–2	3	6
General condition at 48 h	0–2	3	6

## Results

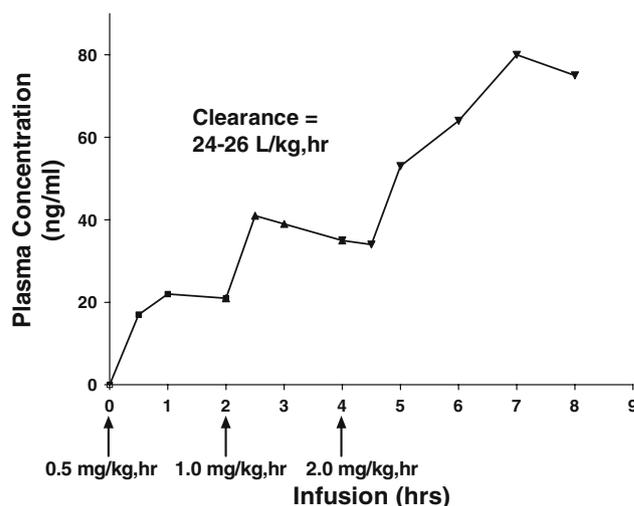
### Pharmacokinetic studies

To achieve steady state concentrations in plasma, continuous infusion of the drug was used. At a steady state, the rate of infusion is by definition equal to the rate of elimination of the drug, i.e. the infusion rate is equal to the total plasma clearance value ( $CL_p$ ) multiplied by the steady state concentration ( $C_{ss}$ ):

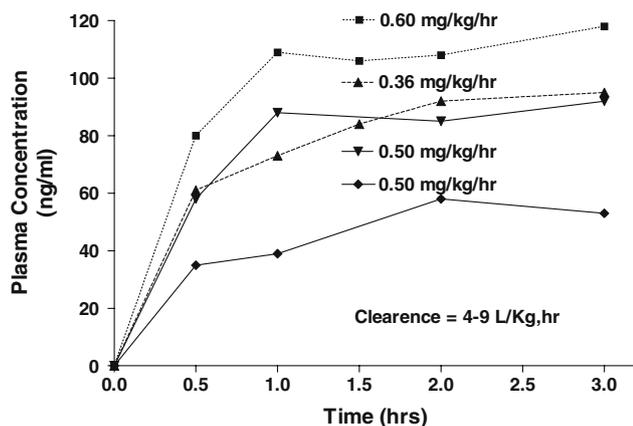
$$\text{Infusion Rate} = CL_p \times C_{ss}. \quad (a)$$

At given infusion rate and steady state concentration, the total plasma clearance value can be calculated from these two parameters using the above equation. Following an infusion of caramiphen to a monkey at a rate of 0.5  $\mu\text{g}/\text{kg},\text{min}$  (see Fig. 1), caramiphen concentration in the plasma stabilized after 2 h at approximately 20 ng/ml. At this point, doubling the infusion rate doubled the steady state concentration to around 40 ng/ml and then after an additional doubling from 40 to around 80 ng/ml. The total plasma clearance value for this specific monkey was calculated from these results and Eq. a as 24–26 l/kg h.

In dogs, steady state concentration was obtained following 2 h of a continuous iv infusion. The rates were adjusted to achieve the concentration range expected in humans (see Fig. 2). Individual variations between the animals (total plasma clearance varied in the range of 4–9 l/kg h) resulted in variation of the concentrations obtained at steady state with similar infusion rates. Therefore, in cases where a specific precise concentration is required, a detailed pharmacokinetic study in the



**Fig. 1** Caramiphen plasma concentrations during continuous iv infusion, using three different infusion rates, in the same monkey



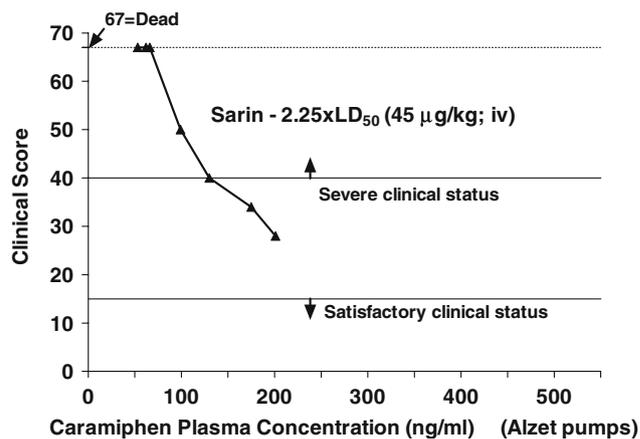
**Fig. 2** Individual caramiphen plasma concentrations during continuous iv infusion to four different dogs

studied animal should precede the protection study, with a 2-week washout period between the studies. This approach may minimize the number of animals required for such studies.

#### Protection studies

Once the clearance value is established for a given animal, the infusion rate can be adjusted to approximate any desired concentration at steady state. Whenever the flow rate has to be kept constant (as in using Alzet mini-pumps), the required infusion rate defines in fact the concentration of the drug that should be used in the Alzet at a specific flow (given by the mini-pump specifications).

This approach is demonstrated in the following study in dogs. Alzet mini-pumps containing caramiphen solution (2 ml each, delivery rate 10  $\mu$ l/h, concentration < 200 mg/ml, adjusted to fit the various dose rates) were implanted subcutaneously for 48 h under aseptic conditions, following mild sedation of the animals (Xylazine, 2 mg/kg iv) combined with local anesthesia (Lidocaine 2%, 1 ml sc). Pyridostigmine (0.1 mg/kg im) was injected repeatedly twice a day, mornings and evenings. This dose of pyridostigmine, which was also used in monkeys, was found to provide adequate protection in various species against OP poisoning (unpublished data). Intravenous exposure of the treated dogs after 48 h to 2.25LD<sub>50</sub> of sarin (45  $\mu$ g/kg) revealed a correlation between caramiphen plasma concentrations and the clinical score following exposure (see Fig. 3). The higher the concentration of the drug, the better was the clinical state. At the plasma concentrations that lead to no adverse effects in humans (70–100 ng/ml) a reduction in severity score was noted but satisfactory protection was not achieved at



**Fig. 3** Correlation between the clinical severity scores and caramiphen plasma concentrations in dogs following an iv exposure to 45  $\mu$ g/kg of sarin. Caramiphen was continuously delivered from implanted Alzets mini pumps starting 48 h prior to the exposure. Last pyridostigmine injection (0.1 mg/kg, im) was administered 20 min before the exposure. Each point represents a single animal

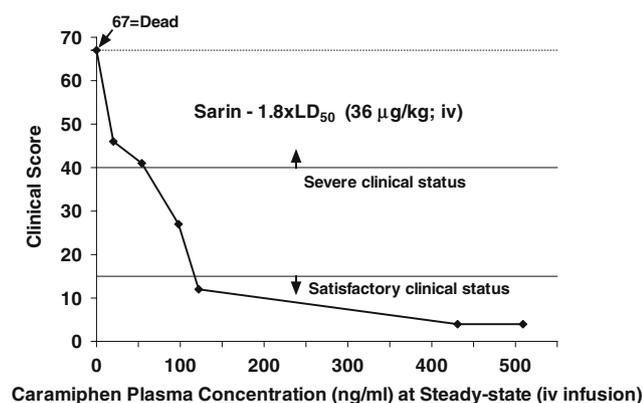
this level of exposure. The dose of the nerve agent was, therefore, lowered in the following study, as well as the concentration of caramiphen in plasma.

Based on clearance measurements, caramiphen infusions rates were adjusted to aim at a steady state concentration-range expected to be used in humans (e.g., a dog with a clearance rate of 5.6 l/kg h was given 0.45 mg/kg h and a dog with a clearance rate of 9 l/kg h was given 0.65 mg/kg h, see Table 2). Following 2 h of infusion, the dogs were exposed to 1.6LD<sub>50</sub> of sarin (32  $\mu$ g/kg; iv). It was thus established that caramiphen plasma concentrations in the range of 60–80 ng/ml (Table 2, last 4 lines) conferred excellent protection against this exposure level.

Another study in monkeys provided similar results. Caramiphen concentrations in plasma around 100 ng/ml conferred adequate protection against 1.8LD<sub>50</sub> of

**Table 2** Clinical scores for dogs exposed to 1.6LD<sub>50</sub> of sarin, after 2 h of caramiphen iv infusion and a single im injection of pyridostigmine (0.1 mg/kg)

Caramiphen infusion rate (mg/kg h)	Caramiphen plasma conc. at the exposure time (ng/ml)	Clinical score
0.42	46	21
0.45	79	8
0.65	58	6
0.81	78	2
0.83	64	2



**Fig. 4** Correlation between the clinical scores following iv exposure to 36 µg/kg of sarin and caramiphen plasma concentrations in monkeys. Caramiphen was administered via iv infusion starting 2 h before the exposure. Pyridostigmine was injected (0.1 mg/kg, im) 20 min before the exposure. Each point represents a single animal

sarin, but lower concentrations were insufficient (see Fig. 4). At the higher caramiphen concentrations the figure resembles the classic S shape dose–response curve.

## Discussion

As previously stated, the extrapolation from animal data to the expected effects in humans has been one of the basic problems in pharmacological and toxicological studies for many years (e.g. see Rall 1969; Levy 1987), and is especially critical in OP poisoning studies (e.g. see Burton 2003). Various species may differ in both the affinity and distribution of the receptors involved in the response to a drug, as well as in pharmacokinetic parameters. Among the latter, the most important are differences in absorption and distribution, variability of the activity and capacity of enzymes that cause biotransformation of the drug, variation in blood–brain barrier penetration and different physiological responses.

One of the methods, used to scale doses across species, is by comparing the administered dose per body weight (i.e. mg/kg). In clinical situations this method is applicable only rarely. A simple correction that has been adopted in pharmacological and toxicological studies relates the dose to the surface area of the treated individual ( $\sim\text{mg}/\text{kg}^{2/3}$ ). This approach is frequently used in human therapy, for pediatric dosage as well as in chemotherapy, mostly to avoid toxic overdose (e.g. see Bailey and Brairs 1996). The equation  $Y = aW^b$  was used for interspecies scaling in var-

ious studies dealing mostly with toxicology data, in which  $Y$  is the physiological variable,  $W$  is body weight,  $a$  and  $b$  are the  $y$ -intercept and the slope of the plot of  $\log Y$  versus  $\log W$ , correspondingly (Mordenti 1986a). Some researchers noted that the effects of certain drugs in various animal species were similar at identical plasma concentrations (although the doses needed to produce these concentrations varied greatly) (Mordenti 1986b).

A more functionally based method compares the doses that lead in various species to a similar effect. For example, the dose of carbamates that inhibits 20–40% of erythrocyte acetylcholinesterase was accepted as adequate for the protection of various species against nerve agents (e.g. see Dunn and Sidell 1989; Meshulam et al. 1995, 2001). Behavioral and physiological minimal effective doses (MED) of various anticholinergic drugs, in comparison to their protection ratio, were used to rate their relative prophylactic efficacy (Raveh et al. 1996). The dose of midazolam leading to mild sedation may be used to predict its anticonvulsive efficacy in the same species exposed to OPs (E. Gilat et al., unpublished results). However, such an approach could sometimes be misleading, because different central effects might be related to different receptors and/or activated by different brain regions. In a human study of 15 subjects with various midazolam doses, it has been found that  $C_{\text{max}}$  was proportional to the administered dose, and the degree of sedation was significantly correlated to midazolam plasma levels (Behne et al. 1989).

Nakashima et al. (1987) suggested a physiologically based pharmacokinetic model, derived by using plasma unbound concentrations, in order to predict the human plasma concentration of biperidin based on animal studies. Since biperidin is exclusively eliminated by the liver, they used the drug's hepatic intrinsic clearance for interspecies scaling. In this manuscript, we present another approach for extrapolation from animal studies in the case of anticholinergic drugs, based on a comparison of plasma concentrations at steady state.

Steady state concentrations, achieved by continuous infusion, were essential to establish a reasonable correlation between the measured plasma concentration and the protective effect. In order to minimize the number of large animals needed for such studies, evaluation of clearance parameters in the specific animal studied was instrumental for establishing in later experiments the desirable plasma concentrations.

The data for total plasma clearance values, for both dogs and monkeys, did not fit nicely to the  $Y = aW^b$  relationship, which indicated the need for a different interspecies scaling method. By comparing the data

from dogs (Table 2) and monkeys (Fig. 4), it was established that the concentration range of caramiphen in plasma, which seems acceptable for humans (70–100 ng/ml), might confer, when combined with pyridostigmine pretreatment, reasonable prophylactic protection against lethal doses of sarin exposure (in the range of 1.6–1.8 LD<sub>50</sub>). The data point out that higher toxic challenge requires comparable shift in the effective caramiphen concentrations, probably not because of the need for longer duration of action (since the protection studies were carried out at steady state) but rather as an indication for the need for a more intense cholinergic blockade.

The methodology presented in this study might be applied to other studies in which the extrapolation from animal studies to the effects in humans is complicated due to ethical considerations. Whenever dose response curves can be compared in two animal models, the extrapolation to the expected pharmacological effects in humans might be considered more reliable.

The protocols of all experiments were examined and approved by the IIBR Committee for Animal Experimentation as required by local law, with emphasis on the prevention of any unnecessary animal suffering. The use of all laboratory animals was carried out according to the recommendations of the Guide for the Care and Use of Laboratory Animals, National Academy Press, Washington, DC, 1996.

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